

## LEFT VENTRICULAR REMODELING AFTER ACUTE MYOCARDIAL INFARCTION

*Marc A. Pfeffer, M.D., Ph.D.*

Department of Medicine, Harvard Medical School, Cardiology Division, Brigham & Women's Hospital, Boston, Massachusetts 02115

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### ABSTRACT

The loss of myocytes as a consequence of myocardial infarction results in a prompt reduction in regional wall motion and often leads to more protracted and progressive changes in ventricular architecture. The recognition that the process of ventricular enlargement following myocardial infarction is modifiable provided the initial rationale for the use of angiotensin-converting enzyme (ACE) inhibitors as therapy to prevent deterioration in ventricular size and function following infarction. Experimental and clinical studies have documented the effectiveness of this therapy in preventing this late enlargement following infarction. Increasing clinical evidence indicates that this new use of ACE inhibitor therapy in survivors of acute myocardial infarction will lead to an improvement in clinical outcome.

### INTRODUCTION

The classic concept that abrupt coronary occlusion simply impairs contraction of the underperfused segment of myocardium has been supplanted by a time-dependent view of regional and global alterations in ventricular performance that are consequent to loss of contractile tissue (1). This broader and more dynamic approach to the alterations in ventricular geometry and performance

following myocardial infarction is the result of complementary animal and clinical studies. These studies have also underscored the importance of these changes in ventricular architecture to overall clinical outcome. In the broadest sense, ventricular remodeling is a general term used to describe the architectural changes in ventricular mass and size that characterize normal growth as well as pathologic hypertrophy. The particular reference to remodeling after myocardial infarction describes the architectural alterations in the ventricle that subsequently result from coronary occlusion and myocardial necrosis. In this chapter, we review the process and time course of ventricular remodeling following infarction. The factors responsible and the potential to modify this particular type of ventricular remodeling are presented, and their relationship to clinical outcomes is discussed.

## INFARCT EXPANSION

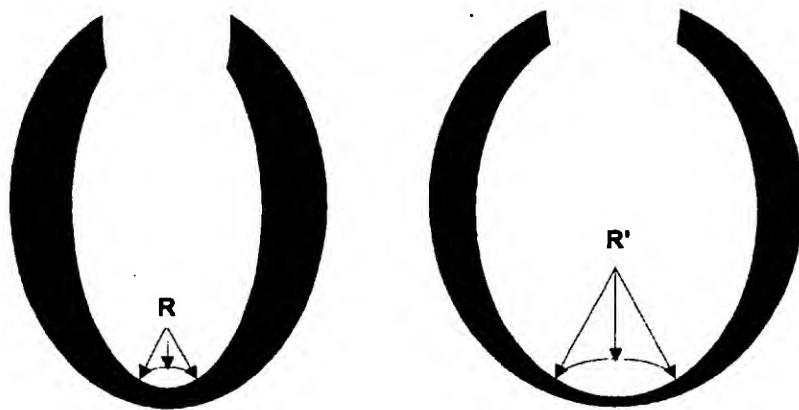
Death of myocytes induced by coronary occlusion or myocardial infarction leads to a sequence of histological alterations in which the necrotic myocytes are replaced by fibrous connective tissue (2). Necrosis of myocytes causes a localized inflammatory response that catabolizes the cellular debris. An overlapping phase of fibroblast proliferation and collagen deposition continues and completes the formation of scar tissue, wherein the remaining viable myocytes within the infarcted region are realigned and attached in a dense collagen matrix. The tensile strength of the affected region is transiently reduced during this period of resorption of necrotic tissue. During this period, the noncontractile wall is most vulnerable to the early structural deformation known as infarct expansion prior to scar formation.

Infarct expansion was originally defined using postmortem examinations of patients dying of acute phase infarction whose left ventricle exhibited regional thinning and elongation in the segment with myocardial necrosis (3). More recently, *in vivo* studies utilizing mainly echocardiographic techniques have assessed the incidence, time course, and consequences of this alteration in ventricular topography in survivors of acute myocardial infarction (4–6). Echocardiographic diagnosis of infarct expansion is generally used to divide the ventricle into anterior and posterior segments based on the internal landmarks of the papillary muscles in the short axis plane. The noncontractile region is designated as the infarct-containing segment, and the length of this segment is compared with that of normal, noninfarcted segments from comparable views.

Infarct expansion is not, however, a complication of all myocardial infarctions. It tends to be more frequent among patients with large transmural infarctions, especially among those with infarctions that involve the apex of the ventricle. The importance of infarct size as a risk factor for infarct expan-

sion and eventual global remodeling is intuitive: More extensive noncontractile segments provide a greater stimulus for segment lengthening and overall ventricular enlargement. Concomitantly, since the histologic basis of infarct expansion is a diminution of the number of viable myocytes across the ventricular wall (7), transmurality is another key determinant of the risk of postinfarct remodeling. Conversely, preservation of myocytes within the infarcted region is a deterrent to this structural change.

The vulnerability of myocardial infarctions involving the ventricular apex to expansion is particularly noteworthy, since it underscores the relationship of regional wall stress to the architectural changes (8). Given the normal ellipsoid shape of the ventricle, the apex is the most highly curved as well as the thinnest region and has the lowest wall tension. Because of this difference in the radius of curvature, this thinner wall has the same wall stress (tension per unit muscle thickness) as the rest of the myocardium under normal conditions. However, loss of contractile function in this region results in an immediate



#### Law of Laplace

$$T = \frac{PR}{2}$$

#### Wall Stress ( $\sigma$ )

$$\sigma = \frac{T}{h}$$

*Figure 1* Ventricular wall tension and thickness is normally lowest at the apex, the region with the greatest curvature. However, as illustrated on the right, if the apex is involved in the process of elongation, the increase in radius at this normally thinned area results in markedly increased wall stress. T, tension; P, pressure; R, radius; h, thickness. (Figure courtesy of Gary F. Mitchell, M.D.).

change in the regional curvature. This change exposes the thinned, poorly contracting myocardium to a marked increase in mechanical stress which, in turn, leads to a propagation of infarct expansion (Figure 1). Because apical infarctions generally involve the left anterior descending coronary artery, which also supplies a larger myocardial territory, it has been difficult to distinguish local shape from more extensive infarction as factors that increase the likelihood of this region for infarct expansion. However, a well-controlled study in dogs revealed greater infarct segment lengthening in the apex with occlusion of the left anterior descending coronary artery compared with an infarcted segment of the posterior myocardium with circumflex coronary artery occlusion, even when comparable wall-motion abnormalities were experimentally produced (9).

Patients who experience an acute myocardial infarction and exhibit echocardiographic evidence of infarct expansion are at greater risk of clinical complications, including acute myocardial rupture (4, 6, 10, 11). More commonly, however, the clinical complications of infarct expansion are manifest in the long term by congestive heart failure, aneurysm formation, additional myocardial ischemic events, and premature cardiovascular mortality. These long-term consequences are better understood when infarct expansion is viewed as the beginning of a time-dependent process of global ventricular remodeling that follows myocardial infarction (1).

## GLOBAL VENTRICULAR ENLARGEMENT

Although early investigations of ventricular remodeling following infarction focused on the infarct-containing segment, a number of important studies have underscored the alterations in performance and morphology in the remote noninfarcted regions. A detailed study of sequential alterations in regional myocardial function in the dog (12) confirmed the anticipated abrupt loss of function in the zone perfused by the occluded coronary artery, as was first described by Tennant & Wiggers in 1935 (13). In addition, the modern study showed that the uninfarcted region remote from the territory of coronary occlusion had increased relative shortening and greater end-diastolic lengths (12). Clinical studies have also reported this lengthening of the noninfarcted zone following serial evaluations in the weeks to months after infarction (6, 14). Although these changes in the noninfarcted region are not as abrupt or as obvious in the acute phase, their contribution to the late insidious dilatation of the ventricle that follows myocardial infarction is significant (15, 16).

The rat model of coronary occlusion has been extremely useful in delineating pathophysiology of progressive ventricular enlargement following myocardial infarction (17). This model generally involves the left ventricular free wall with transmural infarctions. By delineating the time course of chamber

enlargement and controlling for infarct size and cavity distension, cavity enlargement appears to be primarily due to structural alterations in the ventricle, many of which occurred after necrotic myocardium had been replaced with an extensive deposition of collagen (18). Convincing clinical data indicate that in at least some selected survivors of myocardial infarction, progressive enlargement continues well beyond the early time period of infarct expansion (15, 16, 19–21). Indeed, the late process of ventricular remodeling appears to be predominantly a consequence of elongation of the contractile zone and of further distortion of ventricular shape, with little change in the length of the initial dyskinetic segment (15). This newfound knowledge of time-dependent alterations in regional and global ventricular topography and in overall cavity size has expanded the paradigm for treatment of survivors of acute myocardial infarction from the all-important initial phase of reducing the extent of necrosis to a more protracted phase of limiting secondary remodeling following infarction.

#### *Enlargement and Short-Term Adaptation of Pump Function*

Prompt reduction in regional wall motion results in an almost immediate decline in ejection fraction and a concomitant reduction in stroke volume. The extent of akinesis and dyskinesis and the reduction in ejection fraction are closely related (22–26). The geometric response of enlargement can lead to restoration of stroke volume without concomitant improvement in ejection fraction. Indeed, when 20% of the circumference of the left ventricle is noncontractile, normal stroke volume cannot be sustained without ventricular enlargement (27). Therefore, enlargement itself in the early phase may help restore global pump function in the presence of a large noncontractile segment and reduced ejection fraction. This is precisely what McKay et al found (14). They demonstrated that from day one to two weeks after infarction, the ventricular enlargement process was associated with the restoration of pump function without concomitant increases in filling pressure (14). Detailed hemodynamic assessment of survivors of first anterior infarcts who were selected for depressed left ventricular ejection fraction showed that systemic hemodynamics were basically normal three weeks after the initial insult despite marked wall-motion abnormalities and depression of ejection fraction (28). This restoration of pump function of the impaired ventricle was accomplished from a wedge pressure of only 14 mm Hg and marked ventricular enlargement. A normal stroke volume can be produced by the larger ventricular cavity with less muscle excursion and less change in chamber radius (27).

#### *Long-Term Maladaptive Enlargement*

The downside of this initial compensation, which used the altered geometry (enlargement) to restore stroke volume, is that the architectural changes create

greater loading conditions on the viable myocardium that promote further enlargement as well as hypertrophy and dysfunction. During the ejection phase, the normal increase in systolic pressure is accompanied by wall thickening and a reduction in radius. The increase in wall thickness and reduction in chamber radius more than offset the rise in pressure, as wall tension actually falls during ejection (29). The opposite pattern of increasing wall tension during ejection is seen in the remodeled postinfarction ventricle (30). This delicate balance between restoration of pump function and augmentation of subsequent work load potentially creates a vicious cycle wherein dilatation can be viewed as an initial compensation that becomes a major detriment in the long run as a consequence of unfavorable loading conditions.

Like enlargement, distortion of ventricular shape is common in postinfarct remodeling. This distortion occurs in conjunction with expansion and continues throughout the enlargement process, imposing an additional mechanical disadvantage. Moreover, extensive infarcts can result in loss of normal ellipticalization of the ventricle with systolic contraction, resulting in an additional disadvantage over and above the loss of contractility (31). It is therefore not surprising that measures of the extent of ventricular enlargement and distortion are among the most sensitive predictors of clinical outcomes in survivors of myocardial infarction (32–34).

## MODIFICATION OF VENTRICULAR REMODELING FOLLOWING INFARCTION

In the broadest sense, intervention in remodeling following infarction involves three separate but complementary strategies. The most important strategy is the use of primary preventive measures to reduce the initial risk of myocardial infarction. Modification of risk factors for the atherosclerotic process is the mainstay of fundamental long-term therapy. However, patients that experience a myocardial infarction have several opportunities for favorable modification of ventricular remodeling. Since infarct size and transmurality are major factors for ventricular remodeling, the second strategy comprises early-intervention measures to limit the extent of damage. Prompt restoration of coronary flow within the period of myocyte salvage provides long-term benefit by reducing the extent of wall-motion abnormalities and preserving ventricular function, thereby limiting the risk of progressive enlargement. Recognition of progressive enlargement occurring late after infarction serves as the basis for a third mechanistic modality, which involves favorable modification of the remodeling that follows infarction. Progressive ventricular enlargement can be considered a failure of risk factor modification and myocyte salvage. The potential for modification of progressive ventricular enlargement following myocardial infarction is the subject of the remainder of the discussion.

It is now apparent that, independent of myocyte salvage, factors that alter infarct healing or mechanical deforming forces can either exacerbate or attenuate the enlargement process following infarction (1). Reestablishment of patency of the infarct-related vessel offers the obvious benefit of salvaging myocytes and reducing infarct size, which in turn reduces the risk of further enlargement. However, increasing evidence indicates that even late coronary reperfusion (beyond a time window for myocyte salvage) can help limit ventricular deformation (35–38). Patients with successful reperfusion or good collateral flow to the infarct zone are less likely to develop aneurysms (39) or to exhibit progressive global ventricular enlargement with long-term follow-up (28, 40). In animal studies, where the distinction between reperfusion with and without salvage is more readily obtainable, a favorable effect of reperfusion on ventricular topography independent of overt salvage was identified (35, 36, 38).

Even in transmural infarctions, regions of viable myocytes can clearly be found within the infarcted zone, and patency or collateral flow could contribute to the viability of these contractile cells without altering the overall assessment of infarct size (38). Although a patent coronary artery supplying the infarct territory is generally associated with less ventricular enlargement, clinical benefits of late intervention to restore coronary artery patency have not been unequivocally established by prospectively designed placebo-controlled studies (41).

### *ACE Inhibition*

Using the rationale that the architectural changes in the ventricle that occur following myocardial infarction primarily result from sustained elevations in wall stress, early studies in an experimental model sought to determine whether long-term therapy with an angiotensin-converting enzyme (ACE) inhibitor would modify the time-dependent process of ventricular enlargement (42). In the animal studies, the global process of ventricular enlargement that is a sequela of myocardial infarction could indeed be attenuated by chronic administration of an ACE inhibitor (42, 43). Reduction of left ventricular filling pressure appears to be an important component of this structural change, since comparable arterial pressure reduction with hydralazine did not reduce the filling pressure or have the favorable structural effect of attenuating ventricular remodeling (43). ACE inhibitors exert a number of effects (e.g. modification of intrarenal hemodynamics and blood volume, reduced neurohormonal stimulation, and direct trophic actions on the myocyte and vascular components of the heart), all of which may contribute to their beneficial effects on ventricular structure and function.

These observations in animal studies had particular relevance in humans, since ACE inhibitor therapy had also been clinically shown to attenuate re-

modeling following infarction (28, 40). Early studies that selected patients for reduced ejection fraction confirmed the progressive enlargement process in conventionally treated survivors of myocardial infarction and showed that the addition of an ACE inhibitor led to a reduction in this ventricular enlargement. Extensive data now indicate that, in patients at risk for enlargement, treatment with an ACE inhibitor can attenuate the enlargement process (44–47).

### *Clinical Outcome Studies*

Although attenuation of enlargement is mechanistically interesting, justification for treatment must be based on clinical outcomes rather than on the presumed surrogate marker of reduced enlargement. Using the rationale that attenuation of enlargement would improve clinical outcome, a series of international clinical trials evaluated the effects of ACE inhibitor therapy on survival and future cardiovascular events in patients who have experienced acute myocardial infarction. These trials can be divided into two categories based on the design feature of patient selection (Table 1): (a) studies that selected patients for either clinical or objective measures associated with higher risk for cardiovascular complications, or (b) studies that tested a much broader use of ACE inhibition therapy during acute myocardial infarction.

Studies that selected patients either for objective evidence of ventricular dysfunction (48) or for clinical indications of signs and symptoms of congestion (49) have shown a consistent benefit of ACE inhibitors in prolonging

**Table 1** ACE inhibitor use in acute myocardial infarction<sup>a</sup>

Study	Selective			
	Number	Duration (months)	RR%	Lives saved/1000
SAVE	2231	42	19	42
AIRE	2006	15	27	57
SMILE	1556	1 12	(22) 33	18 41
TRACE	1749	24	22	76
Broad Inclusion				
CONSEN II	6090	5	0	—
GISSI 3	19394	1.5	12	8
ISIS 4	58043	1	7	5
Chinese	NA	—	NA	NA

<sup>a</sup>RR, risk reduction. All designated risk reduction percentages are significant except SMILE at 1.5 months. NA, not available. SAVE (48), Survival and Ventricular Enlargement; AIRE (49), Acute Infarction Ramipril Efficacy; SMILE, Survival of Myocardial Infarction Long-term Evaluation; TRACE, Trandolapril in Patients with Reduced Left Ventricular Function After Myocardial Infarction; CONSEN II, Second Cooperative North Scandinavian Enalapril Survival Study; GISSI 3, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio; ISIS4, Fourth International Study of Infarct Survival.

survival and reducing other cardiovascular complications. The broader inclusion of studies that for the most part required only adequate blood pressure levels and clinical stability and that began ACE inhibition therapy within the first day of the infarct also yielded a significant survival benefit. However, the magnitude of benefit in these latter studies was not as great. ACE inhibition therapy in a broad acute myocardial infarction population saved approximately five lives per thousand patients treated. This figure represents the pooled experience; higher-risk subgroups, e.g. patients with prior myocardial infarction or infarcts shown electrocardiographically to involve the anterior wall, appeared to derive greater benefit from treatment.

Another important difference in the design of the selective vs the broad eligibility trials was the duration of follow-up, which was much shorter in the broad trials than in the more selective trials. This discrepancy makes direct comparisons difficult. However, the consensus based on the evidence from all these trials is that high-risk patients clearly benefit from ACE inhibitors and should therefore be treated indefinitely. Use of ACE inhibitors in a non-selected population of patients following myocardial infarction is for the most part safe and does offer some measurable improvement in survival over and above that conferred by current conventional therapy for acute myocardial infarction.

Although the theme of this review is ventricular remodeling, whether the benefits associated with long-term ACE inhibition therapy for survivors of myocardial infarction are related solely to attenuation of enlargement remains unclear. In the Survival and Ventricular Enlargement (SAVE) Study, a substantial cohort was examined with serial echocardiographic studies (50). In this group, progressive enlargement was indeed shown to be associated with a higher likelihood of adverse cardiovascular events. Attenuating enlargement with ACE inhibitor therapy reduced this risk. However, other mechanisms of benefit for long-term ACE inhibition therapy are clearly operative. Both the Studies of Left Ventricular Dysfunction (SOLVD) (51) and the SAVE study (52) indicated that clinical reports of myocardial infarction were fewer with ACE inhibition therapy. This protective effect from coronary atherosclerotic events was not related to the level of left ventricular dysfunction in either of these highly selected patient populations.

## SUMMARY

Risk factors for cardiovascular events are epidemiologically important and become operationally important as well when their modification results in clinical benefit. Progressive enlargement following infarction can now be considered a modifiable risk factor. As with all other risk factors, progressive enlargement must be more thoroughly investigated in order to identify the

population that will derive optimal benefit from therapy. As additional mechanistic information becomes available, further studies will also be required to determine how this risk factor adversely affects outcome. Although progressive left ventricular enlargement can now be added to the list of modifiable risk factors for survivors of myocardial infarction, considerable investigation will be required to optimally utilize this information in appropriate patients and to develop a more precise understanding of the mechanisms underlying these benefits.

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### Literature Cited

- Pfeffer MA, Braunwald E. 1990. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* 81:1161-72
- Fishbein MC, MacLean D, Maroko PR. 1978. The histologic evolution of myocardial infarction. *Chest* 73:843-49
- Hutchins GM, Bulkley BH. 1978. Infarct expansion versus extension: two different complications of acute myocardial infarction. *Am. J. Cardiol.* 41:1127-32
- Eaton LW, Weiss JL, Bulkley BH, et al. 1979. Regional cardiac dilatation after acute myocardial infarction. Recognition by two-dimensional echocardiography. *New Engl. J. Med.* 300:57-62
- Weiss JL, Bulkley BH, Hutchins GR, Mason SJ. 1981. Two-dimensional echocardiographic recognition of myocardial injury in man: comparison with postmortem studies. *Circulation* 63:402-8
- Erlebacher JA, Weiss JL, Weisfeldt ML, Bulkley BH. 1984. Early dilation of the infarcted segment in acute transmural myocardial infarction: role of infarct expansion in acute left ventricular enlargement. *J. Am. Coll. Cardiol.* 4:201-8
- Weisman H, Bush D, Mannisi J, et al. 1988. Cellular mechanisms of myocardial infarct expansion. *Circulation* 78:186-91
- Pirolo JS, Hutchins GM, Moore GW. 1986. Infarct expansion: pathologic analysis of 204 patients with a single myocardial infarct. *J. Am. Coll. Cardiol.* 7:349-54
- Picard MH, Wilkins GT, Gilliam LD, et al. 1991. Immediate regional endocardial surface expansion following coronary occlusion in the canine left ventricle: disproportionate effects of anterior versus inferior ischemia. *Am. Heart J.* 121:753-62
- Schuster EH, Bulkley BH. 1979. Expansion of transmural myocardial infarction: a pathophysiologic factor in cardiac rupture. *Circulation* 60:1532-38
- Weisman HF, Healy B. 1987. Myocardial infarct expansion, infarct extension, and reinfarction: pathophysiologic concepts. *Prog. Cardiovasc. Dis.* 30:73-110
- Theroux P, Ross J Jr, Franklin D, et al. 1977. Regional myocardial function and dimensions early and late after myocardial infarction in the unanesthetized dog. *Circ. Res.* 40:158-65
- Tennant R, Wiggers CJ. 1935. The effect of coronary occlusion on myocardial contraction. *Am. J. Physiol.* 112:351-61
- McKay RG, Pfeffer MA, Pasternak RC, et al. 1986. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation* 74:693-702
- Mitchell GF, Lamas GA, Vaughan DE, Pfeffer MA. 1992. Left ventricular remodeling in the year following first anterior myocardial infarction: a quantitative analysis of contractile segment lengths and ventricular shape. *J. Am. Coll. Cardiol.* 19:1136-44
- Rumberger JA, Behrenbeck T, Breen JR, et al. 1993. Nonparallel changes in global left ventricular chamber volume and muscle mass during the first year after transmural myocardial infarction in humans. *J. Am. Coll. Cardiol.* 21:673-82
- Fletcher PJ, Pfeffer JM, Pfeffer MA, Braunwald E. 1981. Left ventricular diastolic pressure-volume relations in rats with healed myocardial infarction: effects on systolic function. *Circ. Res.* 49:618-26
- Pfeffer JM, Pfeffer MA, Fletcher PJ, Braunwald E. 1991. Progressive ventricu-

- lar remodeling in rat with myocardial infarction. *Am. J. Physiol.* 260:H1406-14
19. Kostuk WJ, Kazamias TM, Gander MP, et al. 1973. Left ventricular size after acute myocardial infarction: serial changes and their prognostic significance. *Circulation* 47:1174-79
  20. Gaudron P, Eilles C, Kugler I, Ertl G. 1993. Progressive left ventricular dysfunction and remodeling after myocardial infarction: potential mechanisms and early predictors. *Circulation* 87:755-63
  21. Gadsboll N, Hoilund-Carlsen PF, Badsberg JH, et al. 1989. Late ventricular dilatation in survivors of acute myocardial infarction. *Am. J. Cardiol.* 64:961-66
  22. Pfeffer MA, Pfeffer JM, Fishbein MC, et al. 1979. Myocardial infarct size and ventricular function in rats. *Circ. Res.* 44:503-12
  23. Hamilton GW, Murray JA, Kennedy JW. 1972. Quantitative angiocardiology in ischemic heart disease. The spectrum of abnormal left ventricular function and the role of abnormally contracting segments. *Circulation* 45:1065-80
  24. Kitamura A, Kay JH, Krohn BG, et al. 1973. Geometric and functional abnormalities of the left ventricle with a chronic localized noncontractile area. *Am. J. Cardiol.* 31:701-7
  25. Hori M, Inoue M, Mishima M, et al. 1977. Infarct size and left ventricular ejection fraction in acute myocardial infarction. *Jpn. Circ. J.* 41:1299-309
  26. Swan HJC, Forrester JS, Diamond G, et al. 1972. Hemodynamic spectrum of myocardial infarction and cardiogenic shock. A conceptual model. *Circulation* 45:1097-110
  27. Klein MD, Herman MV, Gorlin R. 1967. A hemodynamic study of left ventricular aneurysm. *Circulation* 35:614-30
  28. Pfeffer MA, Lamas GA, Vaughan DE, et al. 1988. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *New Engl. J. Med.* 319:80-86
  29. Weber KT, Janicki JS. 1979. The heart as a muscle-pump system and the concept of heart failure. *Am. Heart J.* 98:371-84
  30. Capasso J, Zhang P, Anversa P. 1992. Heterogeneity of ventricular remodeling after acute myocardial infarction in rats. *Am. J. Physiol.* 262:H486-H495
  31. Mitchell GF, Pfeffer MA. 1995. The role of geometry in left ventricular remodeling following myocardial infarction. *Cardiol. Rev.* In press
  32. Meizlish JL, Berger HJ, Plankey M, et al. 1984. Functional left ventricular aneurysm formation after acute anterior transmural myocardial infarction: incidence, natural history, and prognostic implications. *New Engl. J. Med.* 311:1001-6
  33. White HD, Norris RM, Brown MA, et al. 1987. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 76:44-51
  34. Hammermeister KE, DeRouen TA, Dodge HT. 1979. Variables predictive of survival in patients with coronary disease: selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation* 59:421-30
  35. Hochman JS, Choo H. 1987. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. *Circulation* 75:299-306
  36. Hale SL, Kloner RA. 1988. Left ventricular topographic alterations in the completely healed rat infarct caused by early and late coronary artery reperfusion. *Am. Heart J.* 116:1508-13
  37. Force T, Kemper A, Leavitt M, Parisi AF. 1988. Acute reduction in functional infarct expansion with late coronary reperfusion: assessment with quantitative two-dimensional echocardiography. *J. Am. Coll. Cardiol.* 11:192-200
  38. Brown EJ Jr, Swinford RD, Gadde P, Lillis O. 1991. Acute effects of delayed reperfusion on myocardial infarct shape and left ventricular volume: a potential mechanism of additional benefits from thrombolytic therapy. *J. Am. Coll. Cardiol.* 17:1641-50
  39. Hirai T, Fujita M, Nakajima H, et al. 1989. Importance of collateral circulation for prevention of left ventricular aneurysm formation in acute myocardial infarction. *Circulation* 79:791-96
  40. Sharpe N, Smith H, Murphy J, Hannan S. 1988. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1:255-59
  41. Kim C, Braunwald E. 1993. Potential benefits of late reperfusion of infarcted myocardium. The Open Artery Hypothesis. *Circulation* 88:2426-36
  42. Pfeffer JM, Pfeffer MA, Braunwald E. 1985. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ. Res.* 57:84-95
  43. Raya TE, Gay RG, Aguirre M, Goldman S. 1989. Importance of venodilatation in prevention of left ventricular dilatation after chronic large myocardial infarction in rats: a comparison of captopril and hydralazine. *Circ. Res.* 64:330-37
  44. Sharpe N, Smith H, Murphy J, et al. 1991. Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. *Lancet* 337:872-76

45. Bonaduce D, Petretta M, Arrichello P, et al. 1992. Effects of captopril treatment on left ventricular remodeling and function after anterior myocardial infarction: comparison with digitalis. *J. Am. Coll. Cardiol.* 19:858-63
46. Ray SG, Pye M, Oldroyd KG, et al. 1993. Early treatment with captopril after acute myocardial infarction. *Br. Heart J.* 69:215-22
47. Foy SG, Crozier IG, Turner JG, et al. 1994. Comparison of enalapril versus captopril on left ventricular function and survival three months after acute myocardial infarction (the "PRACTICAL" study). *Am. J. Cardiol.* 73:1180-86
48. Pfeffer MA, Braunwald E, Moye LA, et al. 1992. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *New Engl. J. Med.* 327:669-677
49. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. 1993. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 342:821-28
50. St. John Sutton M, Pfeffer MA, Plappert T, et al. 1994. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction: the protective effects of captopril. *Circulation* 89:68-75
51. Yusuf S, Pepine CJ, Garces C, et al. 1992. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 340:1173-78
52. Rutherford JD, Pfeffer MA, Moye LA, et al. 1994. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *Circulation* 90:1731-38

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## Preamble

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the management or prevention of disease. Rigorous and expert analysis of the available data documenting relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and impact the overall cost of care favorably by focusing resources on the most effective strategies.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly engaged in the preparation of such guidelines in the area of cardiovascular disease since 1980. This effort is directed by the ACC/AHA Task Force on Practice Guidelines, which is charged with developing and revising practice guidelines for important cardiovascular diseases and procedures. Experts in the subject under consideration are selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical provider and specialty groups when appropriate. Writing groups are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular

treatment or procedure, and include estimates of expected health outcomes in areas where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, along with frequency of follow-up and cost-effectiveness.

These practice guidelines are intended to assist physicians and other healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the physician and patient in light of circumstances specific to that patient.

These guidelines have been officially endorsed by the American Society of Echocardiography, the American College of Emergency Physicians, and the American Association of Critical-Care Nurses.

*James L. Ritchie, MD, FACC  
Chair, ACC/AHA Task Force on Practice Guidelines*

## Executive Summary

### Purpose

These guidelines are intended for physicians, nurses, and allied healthcare personnel who care for patients with suspected or established acute myocardial infarction (MI).

This executive summary of the guidelines, plus a definition of the classes and a summary of recommendations, appears in the November 1, 1996, issue of *Circulation*. The guidelines in their entirety, including the ACC/AHA Class I, II, and III recommendations, are published in the November 1996 issue of the *Journal of the American College of Cardiology*. Beginning with these guidelines, the full text of ACC/AHA guidelines will be published in one journal and the executive summary and summary of recommendations in the other. Reprints of both the full text and the executive summary and summary of recommendations are available from both organizations.

### Prehospital Issues

Each year 900 000 people in the United States experience acute myocardial infarction (MI). Of these, roughly 225 000 die, including 125 000 who die "in the field" before obtaining medical care. Most of these deaths are arrhythmic in etiology. Because early reperfusion treatment of patients with acute MI improves left ventricular (LV) systolic function and survival, every effort must be made to minimize prehospital delay. Indeed, efforts are ongoing to promote rapid identification and treatment of patients with acute MI, including (1) patient education about the symptoms of acute MI and appropriate actions to take and (2) prompt initial care of the patient by the community emergency medical system. In treating the patient with chest pain, emergency medical system personnel must act with a sense of urgency.

### Initial Recognition and Management in the Emergency Department

When the patient with suspected acute MI reaches the emergency department (ED), evaluation and initial management should take place promptly, because the benefit of reperfusion therapy is greatest if therapy is initiated early. The initial evaluation of the patient ideally should be accomplished within 10 minutes of his or her arrival in the ED; certainly no more than 20 minutes should elapse before an assessment is made. On arrival in the ED the patient with suspected acute MI should immediately receive (1) oxygen by nasal prongs; (2) sublingual nitroglycerin (unless systolic arterial pressure is less than 90 mm Hg or heart rate is less than 50 or greater than 100 beats per minute [bpm]); (3) adequate analgesia (with morphine sulfate or meperidine); and (4) aspirin, 160 to 325 mg orally. A 12-lead electrocardiogram (ECG) should also be performed. ST-segment elevation (equal to or greater than 1 mV) in contiguous leads provides strong evidence of thrombotic coronary arterial occlusion and makes the patient a candidate for immediate reperfusion therapy, either by fibrinolysis or primary percutaneous transluminal coronary angi-

plasty (PTCA). Symptoms consistent with acute MI and left bundle branch block (LBBB) should be managed like ST-segment elevation. In contrast, the patient without ST-segment elevation should not receive thrombolytic therapy. The benefit of primary PTCA in these patients remains uncertain.

In comparison with standard medical therapy, thrombolytic therapy exerts a highly significant 21% proportional reduction in 35-day mortality among patients with acute MI and ST elevation, corresponding to an overall reduction of 21 deaths per 1000 patients treated. A powerful time-dependent effect on mortality has been observed in the administration of thrombolytic agents. The greatest benefit occurs when thrombolysis is initiated within 6 hours of the onset of symptoms, although it exerts definite benefit when begun within 12 hours. An estimated 35 lives per 1000 patients treated are saved when thrombolysis is used within the first hour of symptom onset, compared with 16 lives saved per 1000 treated when given 7 to 12 hours after symptom onset. Thrombolysis benefits the patient irrespective of age and gender and the presence of comorbid conditions such as diabetes mellitus, although the degree of benefit varies among patient groups. Thrombolytic therapy is associated with a slightly increased risk of intracranial hemorrhage (ICH) that usually occurs within the first day of therapy. Variables that appear to predict an increased risk of ICH include age greater than 65 years, body weight less than 70 kg, systemic arterial hypertension, and administration of tissue plasminogen activator (TPA).

Primary PTCA may be performed as an alternative to thrombolytic therapy, provided that it can be accomplished in a timely fashion by persons skilled in the procedure and supported by experienced personnel. Prompt access to emergency coronary artery bypass graft (CABG) surgery must also be available if primary PTCA is to be undertaken.

Once reperfusion therapy is initiated, the patient with suspected acute MI should be hospitalized. Subsequent short- and long-term management is similar, irrespective of the appearance of the initial ECG. Thus, following the initial triage decision regarding reperfusion therapy, treatment of the patient whose ECG initially showed ST-segment elevation or presumably new LBBB and who received reperfusion therapy is similar to that for the patient whose initial ECG failed to show ST-segment elevation or LBBB and who did not receive reperfusion therapy.

### Hospital Management

#### The First 24 Hours

Once hospitalized, the patient with acute MI should be continuously monitored by electrocardiography and the diagnosis of acute MI confirmed by serial ECGs and measurements of serum cardiac markers of myocyte necrosis, such as creatine kinase isoenzymes or cardiac specific troponin T or I. The patient should be monitored closely for adverse electrical or mechanical events because reinfarction and death occur most frequently within the first 24 hours. The patient's physical activities should be limited for at least 12 hours, and pain

and/or anxiety should be minimized with appropriate analgesics. Although the use of prophylactic antiarrhythmic agents in the first 24 hours of hospitalization is not recommended, atropine, lidocaine, transcutaneous pacing patches or a transvenous pacemaker, a defibrillator, and epinephrine should be immediately available.

Patients who survive a large anterior MI or who have a LV mural thrombus seen on echocardiography are at high risk of having an embolic stroke. Some data suggest that this risk is reduced by early administration of intravenous heparin. For the patient without a large anterior MI or LV mural thrombus who did not receive reperfusion therapy, there are few data on the benefit of heparin beyond that of aspirin,  $\beta$ -adrenoceptor blocking agents, nitrates, and angiotensin converting enzyme (ACE) inhibitors. For the patient given thrombolytic therapy, the recommendations for subsequent heparin administration are based more on current practice than on evidence and depend on the specific thrombolytic agent. There is only limited evidence that heparin (given intravenously or subcutaneously) is beneficial in the patient who receives a nonspecific fibrinolytic agent such as streptokinase, anisoylated plasminogen streptokinase activator complex (APSAC), or urokinase. When TPA (alteplase) is administered, intravenous heparin increases the likelihood of patency in the infarct-related artery (assessed angiographically), but this may not necessarily lead to improved clinical outcome. Considering the superior performance of accelerated TPA plus intravenous heparin in the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) trial, it seems judicious to give heparin intravenously for at least 48 hours after alteplase is given. When primary PTCA is performed, high-dose intravenous heparin is recommended. Aspirin, 160 to 325 mg daily, initially given in the ED, should be continued indefinitely.

Despite the absence of definitive outcome data, it is reasonable to treat the patient with acute MI and without hypotension, bradycardia, or excessive tachycardia with intravenous nitroglycerin for 24 to 48 hours after hospitalization. Concern exists about oral nitrate preparations in the patient with acute MI because of inability to titrate the dose to effect in an acutely evolving hemodynamic situation, whereas intravenous infusion of nitroglycerin can be titrated successfully with frequent measurement of heart rate and cuff blood pressure. Nitroglycerin should not be used as a substitute for narcotic analgesics that are often required in the patient with acute MI.

The patient with evolving acute MI should receive early intravenous  $\beta$ -adrenergic blocker therapy, followed by oral therapy, provided that there is no contraindication.  $\beta$ -Adrenoceptor blocker therapy should be initiated regardless of whether reperfusion therapy was given, because several studies in the prethrombolytic as well as the thrombolytic era showed that  $\beta$ -adrenoceptor blockers diminish morbidity and mortality. Calcium channel blockers have not been shown to reduce mortality in patients with acute MI, and in certain persons with cardiovascular disease they appear to be harmful. In the patient without ST-segment elevation or LBBB in whom

pulmonary congestion is absent, diltiazem may reduce the incidence of recurrent ischemic events, but its benefit beyond that of  $\beta$ -adrenoceptor blockers and aspirin is unclear. Immediate-release dihydropyridines (eg, nifedipine) are contraindicated in the patient with acute MI.

In the patient with evolving acute MI with ST-segment elevation or LBBB, an ACE inhibitor should be initiated within hours of hospitalization, provided that the patient does not have hypotension or a contraindication. Subsequently, the ACE inhibitor should be continued indefinitely in the patient with impaired LV systolic function (ejection fraction less than 40%) or clinical congestive heart failure (CHF). In patients without complications and no evidence of symptomatic or asymptomatic LV dysfunction by 6 weeks, ACE inhibitors can be stopped. On admission to the hospital, a lipid profile and serum electrolyte concentration (including magnesium) should be measured in all patients.

#### After the First 24 Hours

After the first day in the hospital, the patient with acute MI should continue to receive aspirin 160 to 325 mg/d indefinitely with a  $\beta$ -adrenergic blocker; an ACE inhibitor should be administered for at least 6 weeks. Nitroglycerin should be infused intravenously for 24 to 48 hours, and magnesium sulfate should be given as needed to replete magnesium deficits for 24 hours. For the patient receiving alteplase, it is current practice to give intravenous heparin for an additional 48 hours.

Patients with myocardial ischemia that is spontaneous or provoked in the days to weeks after acute MI, irrespective of whether they received thrombolytic therapy, ordinarily should undergo elective angiographic evaluation, with subsequent consideration of percutaneous or surgical revascularization. There is considerable variability in the use of coronary angiography and catheter interventions among survivors of uncomplicated acute MI with preserved LV systolic function. Although some practitioners routinely perform angiography and PTCA during the days after acute MI in virtually all patients, the available data suggest that such a management strategy does not salvage myocardium nor reduce the incidence of reinfarction or death. Accordingly, coronary angiography and subsequent revascularization should be reserved for survivors of acute MI who have preserved LV systolic function and spontaneous or provoked ischemia.

During hospitalization the patient with acute MI should be closely observed for prompt recognition and management of complications. The patient with recurrent chest pain believed due to pericarditis should receive high-dose aspirin (650 mg every 4 to 6 hours). Recurrent chest discomfort thought to be caused by myocardial ischemia should be treated with intravenous nitroglycerin, analgesics, and antithrombotic medications (aspirin, heparin). Coronary angiography with subsequent revascularization therapy should be considered. The patient with heart failure should receive a diuretic (usually intravenous furosemide) and an afterload-reducing agent. For the patient in cardiogenic shock, consideration should be given to inser-

tion of an intra-aortic balloon pump and emergency coronary angiography, followed by PTCA or CABG. The patient with right ventricular infarction and dysfunction should be treated vigorously with intravascular volume expansion (using normal saline) and inotropic agents if hypotension persists.

In the patient with acute MI, the appearance of atrial fibrillation is often a manifestation of extensive LV systolic dysfunction. If its occurrence causes hemodynamic compromise or ongoing ischemia, direct-current cardioversion should be performed. In the absence of these,  $\beta$ -adrenoceptor blocking agents or digitalis should be given to slow the ventricular response. Episodes of ventricular fibrillation should be treated with immediate direct-current countershock; the same is true for episodes of monomorphic ventricular tachycardia associated with angina, pulmonary congestion, or hypotension. If monomorphic ventricular tachycardia is not accompanied by chest pain, pulmonary congestion, or hypotension, it should be treated with intravenous lidocaine, procainamide, or amiodarone.

The patient with acute MI and symptomatic sinus bradycardia or atrioventricular block should receive atropine. Temporary pacing should be performed in the patient with (1) sinus bradycardia unresponsive to drug therapy, (2) Mobitz type II second-degree atrioventricular block, (3) third-degree heart block, (4) bilateral bundle branch block (BBB), (5) newly acquired BBB, and (6) right or left BBB in conjunction with first-degree atrioventricular block.

Immediate surgical intervention is often required for the patient with (1) failed PTCA with persistent chest pain or hemodynamic instability; (2) persistent or recurrent ischemia refractory to medical therapy who is not a candidate for catheter intervention; (3) cardiogenic shock and coronary anatomy not amenable to PTCA; or (4) a mechanical abnormality leading to severe pulmonary congestion or hypotension,

such as papillary muscle rupture (with resultant mitral regurgitation) or ventricular septal defect (VSD).

### *Preparation for Discharge From the Hospital*

Before hospital discharge or shortly thereafter, the patient with recent acute MI should undergo standard exercise testing (submaximal at 4 to 7 days or symptom limited at 10 to 14 days). This is done to (1) assess the patient's functional capacity and ability to perform tasks at home and work, (2) evaluate the efficacy of the patient's current medical regimen, and (3) stratify risk for a subsequent cardiac event. The incremental value of radionuclide imaging or echocardiography during exercise is uncertain. Although markers of electrical instability such as abnormal baroreflex stimulation or the presence of late potentials on a signal-averaged ECG are associated with increased risk of death, their positive predictive value is low, and appropriate therapy when these findings are observed is yet to be determined.

### *Long-Term Management*

For an indefinite period after acute MI, the patient should continue to receive aspirin, a  $\beta$ -adrenoceptor blocker, and a selected dose of an ACE inhibitor. The patient should be instructed to achieve an ideal weight and educated about a diet low in saturated fat and cholesterol. The patient with a low-density lipoprotein (LDL) cholesterol measurement greater than 130 mg/dL despite diet should be given drug therapy with the goal of reducing LDL to less than 100 mg/dL. Smoking cessation is essential. Finally, the patient should be encouraged to participate in a formal rehabilitation program and ultimately to plan to engage in 20 minutes of exercise at the level of brisk walking at least three times a week.

## Guidelines for the Management of Patients With Acute Myocardial Infarction

### I. Introduction

The ACC/AHA statement "Guidelines for the Early Management of Patients with Acute Myocardial Infarction" was introduced in 1990,<sup>1</sup> following a time during which advances in cardiovascular knowledge and therapies proceeded at a pace and scope remarkable even for this century. A substantial body of knowledge and considerable clinical experience was gained in the last decade, and ACC/AHA leaders believed there was a compelling need to summarize this experience and provide guidelines for appropriate management of patients with acute MI. At that time the authors of the guidelines stated that although they believed they were "shooting at a moving target," enough had been established to develop appropriate guidelines. The guidelines were not intended as a rigid prescription but rather as a guide to be modified by clinical judgment, individual patient needs, and the findings of new studies. Revision of the original guidelines was clearly envisioned.

The current committee was convened by the ACC/AHA Task Force on Practice Guidelines and charged at its first meeting, held November 12, 1994, "to review a critical body of knowledge that has accumulated since 1990 and recommend whatever changes or revisions of the original guidelines that seem appropriate." The committee held seven 2-day meetings, convened 11 conference calls, and concluded its business at a final meeting held March 24, 1996. Pertinent medical literature in the English language was identified by a search of standard library databases for the 5 years preceding guideline development. An estimated 5000 publications were reviewed by committee members during the course of their deliberations. The committee reviewed many documents on the management or aspects of management of patients with acute MI published by other organizations, such as the American College of Chest Physicians, the American College of Physicians, the Canadian Cardiovascular Society, and the European Society of Cardiology; in addition, the committee made every effort to adhere to well-established guidelines such as those for advanced cardiac life support (ACLS) and use of automatic defibrillation.

The committee compiled and ranked the evidence, with the weight of evidence ranked highest (A) if the data were derived from multiple randomized clinical trials involving large numbers of individuals. An intermediate rank (B) was given when the data were derived from a limited number of trials involving comparatively small numbers of patients or from well-conceived data analyses of nonrandomized studies or observational data registries. A lower rank (C) was given when consensus opinion of experts was the primary source of a recommendation. In the interest of ease of use, these evidence ranks are not published in the final document but are available upon request. The analysis of the available evidence, as well as its quality, was critical in making final recommendations and is

developed in the text in detail. Similarly, when no evidence was available, this is noted in the text.

The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention summarize both the evidence and expert opinion and are expressed in the ACC/AHA format as follows:

**Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

**Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

**Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.

**Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.

**Class III:** Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Literature citations were generally restricted to published manuscripts appearing in journals listed in *Index Medicus*. Because of the scope and importance of certain ongoing clinical trials and other emerging information, published abstracts (previously refereed) were cited when they were the only published information available.

The emphasis of the committee's review reflected the current trend in the practice of medicine, which is making a transition from practice patterns driven by pathophysiological and nonquantitative reasoning to a broad belief in "evidence-based medicine." Nowhere has this concept been more firmly embraced than in the treatment of cardiovascular disease, and it was greatly influenced by the recent demonstration in clinical trials that concepts seemingly quite rational and widely accepted have been associated with substantial adverse effects on mortality.<sup>2</sup> Despite the recognized importance of empirical evidence to guide therapeutic decisions, it has been only since the advent of computers that computational and organizational capabilities have begun to meet the need. As a consequence, the medical community is in the rapid growth phase of learning how to assimilate and interpret clinical trials and observational databases.

Although these guidelines have been shaped largely within the context of evidence-based medical practice, the committee clearly understands that variations in inclusion and exclusion criteria from one randomized trial to another impose some limitation on the generalizability of their findings. Likewise, in its efforts to reconcile conflicting data, the committee emphasized the importance of properly characterizing the population under study. Not all patients diagnosed with acute MI are alike. For example, those diagnosed with acute MI on entry into the medical care system differ considerably from those whose diagnosis becomes evident late after admission and appears not as the admission diagnosis but only as the discharge diagnosis. In the former, thrombolytic therapy is feasible, whereas in the latter it is

not. Studies examining "processes of care" in acute MI will be greatly influenced by such considerations.

In the first half of this decade rapid changes in the natural history of patients with acute MI have continued, and the committee recognizes the establishment of the reperfusion era. In this era a constellation of therapies in the management of patients with acute MI has been introduced, and therapy is not limited just to the widespread use of thrombolytic agents, PTCA, and emergency CABG surgery in suitable patients. The reperfusion era also embraces the extensive use of aspirin,  $\beta$ -adrenoceptor blocking agents, vasodilator therapy, and the common use of ACE inhibitors. In addition, this era has witnessed far more aggressive use of cardiac catheterization and revascularization techniques in patients with clinical markers of a poor prognosis (eg, hypotension, CHF, and continuing ischemia). The combined use of all these therapies has resulted in an impressive reduction in early and 1-year mortality for patients with acute MI.

As a consequence of this improved survival rate, patients now under observation, such as those enrolled in recent thrombolysis trials, have low rates for subsequent cardiac events. This substantially reduces the predictive accuracy of many tests previously used in risk stratification. Therefore, many gains have resulted in the need to rethink some diagnostic and therapeutic strategies.

It is the aim of these revised guidelines to reflect what the committee has identified as the most important changes to be made in thinking about patients with acute MI. Many therapies and procedures in current use are not based on sound scientific evidence. The committee proposes the abandonment of such therapies and procedures that can be identified with confidence. On the other hand, new information suggests that a practical division of all patients with acute MI is to classify them as those with ST-segment elevation and those without it. Evidence now shows a distinction in pathoanatomy between the two that demands different therapeutic approaches. Ample evidence exists that persons with suspected MI and ST-segment elevation or BBB should undergo immediate reperfusion, and those without these findings should not.

Committee members were selected from cardiovascular specialists with broad geographical representation and combined involvement in academic medicine and primary practice. The Committee on Management of Acute Myocardial Infarction was also broadened by members of the American Academy of Family Physicians, the American College of Emergency Physicians, the AHA Council on Cardiovascular Nursing, and the American Association of Critical-Care Nurses.

The committee was chaired by Thomas J. Ryan, MD, and included the following members: Jeffrey L. Anderson, MD; Elliott M. Antman, MD; Blaine A. Braniff, MD; Neil H. Brooks, MD; Robert M. Califf, MD; L. David Hillis, MD; Loren F. Hiratzka, MD; Elliot Rapaport, MD; Barbara J. Riegel, DNSc; Richard O. Russell, MD; Earl E. Smith III, MD; and W. Douglas Weaver, MD.

This document was reviewed by three outside reviewers nominated by the ACC and three outside reviewers nominated

by the AHA, as well as individuals from the American Academy of Family Physicians, the American College of Emergency Physicians, the American Association of Critical-Care Nurses, the AHA Council on Cardiovascular Nursing, the American Society of Echocardiography, and the American Society of Nuclear Cardiology.

"ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction" was approved for publication by the governing bodies of the American College of Cardiology and the American Heart Association. These guidelines will be reviewed 2 years after publication and yearly thereafter and considered current unless the task force revises or withdraws them from distribution.

## II. Prehospital Issues

### Recommendations

#### *Class I*

1. Availability of 911 access.
2. Availability of an emergency medical services (EMS) system staffed by persons trained to treat cardiac arrest with defibrillation if indicated and to triage patients with ischemic-type chest discomfort.

#### *Class IIa*

1. Availability of a first-responder defibrillation program in a tiered response system.
2. Healthcare providers educate patients/families about signs and symptoms of acute MI, accessing EMS, and medications.

#### *Class IIb*

1. Twelve-lead telemetry.
2. Prehospital thrombolysis in special circumstances (eg, transport time greater than 90 minutes).

Each year approximately 900 000 persons in the United States experience acute MI, and about 225 000 of them die. At least one half of these persons die within 1 hour of onset of symptoms and before reaching a hospital emergency department.<sup>3,4</sup> It has been recognized for more than 3 decades that the majority of these sudden cardiac deaths are the result of fatal arrhythmias that often can be stopped by emergency cardiopulmonary resuscitation (CPR), defibrillation, and prompt ACLS. More recent data regarding the time-dependent benefits of thrombolytic therapy provide added stimulus to develop more effective means of expediting delivery of medical care to persons with acute MI. It has been shown that early treatment results in reductions in mortality, infarct size, and improved LV function.<sup>5-7</sup> Clearly, delay in treating patients with suspected acute MI is a critical factor in decreasing the overall survival rate. For these reasons the National Heart, Lung, and Blood Institute (NHLBI) has initiated the National Heart Attack Alert Program (NHAAP), a coordinated national program that extends the ACC/AHA

recommendations promoting rapid identification and treatment of patients with acute MI.<sup>8,9</sup>

### *Recognition and Management*

It has been demonstrated that most patients do not seek medical care for 2 hours or more after symptom onset. A sizable proportion wait 12 hours or more. In general, reperfusion therapy beyond 12 hours may offer little benefit.<sup>8,9</sup> The components of delay from symptom onset to treatment are (1) patient related (ie, failure to recognize the seriousness of the problem and delay in seeking emergency care); (2) prehospital evaluation, treatment, and transport times; and (3) time required for diagnosis and initiation of treatment in the hospital. In most cases, patient-related delay is the longest, but each component moves the patient further away from the golden first hour to a time when the effect of treatment is lessened. Effective early intervention cannot occur without appropriate patient and family action early after symptom onset.

### **Intervention Strategies**

Interventions to minimize patient delay are primarily educational in nature and focus on what to do when ischemic-type chest discomfort occurs. Patients with known heart disease or those at high risk of acute MI should be educated by physicians, nurses, and staff about common symptoms of acute MI and appropriate actions to take after symptom onset. Patients should be given an action plan that covers (1) prompt use of aspirin and nitroglycerin if available, (2) how to access EMS, and (3) location of the nearest hospital that offers 24-hour emergency cardiac care. Ideally patients should be given a copy of their resting ECG as a baseline to aid physicians in the emergency department. Because chest discomfort is the most common symptom of infarction,<sup>10</sup> patients need simple instructions to respond effectively. In addition to being made aware that chest discomfort may be more of a pressure sensation than actual pain, they should understand that the discomfort can be referred to the arm, throat, and lower jaw and can be accompanied by breathing difficulty, diaphoresis, or a feeling of impending doom.<sup>11,12</sup> Reviewing the description of possible symptoms and the action plan in simple, understandable terms at each visit is extremely important, because studies have indicated that many patients minimize the importance of their symptoms or deny the possibility of acute MI.<sup>12,13</sup> Discussions with patients should emphasize the importance of acting promptly. Family members should be included in these discussions and enlisted as advocates for action when symptoms of infarction are apparent.<sup>8,11</sup>

The role of medications to be taken at onset of symptoms must be tailored to each individual. Current advice is to take 1 nitroglycerin tablet sublingually at the onset of ischemic-type chest discomfort and another every 5 minutes for a total of 3 doses. If symptoms persist, the patient should call 911 emergency services or obtain other emergency transportation to the hospital—not the physician's office. The hospital should be staffed round-the-clock by physicians and nurses competent in

(1) performing an initial evaluation, including an ECG, (2) providing cardiac monitoring and ACLS, and (3) providing reperfusion therapy. Patients who can be identified in the field as being at high risk with signs of shock, pulmonary congestion, heart rate greater than 100 bpm, and systolic blood pressure less than 100 mm Hg ideally should be triaged to facilities capable of cardiac catheterization and revascularization. Although it has not yet been demonstrated that initial triage of such patients to tertiary centers results in improved outcome compared with initial management in primary facilities, this approach has the desirable effect of obviating the need of emergency transfer of a critically ill patient from one hospital to another, interrupting intensive nursing care and possibly delaying diagnosis and treatment.

Use of the EMS system almost always decreases delays in initiation of definitive care.<sup>8</sup> Accordingly, the physician should discuss the use of 911 or other local emergency numbers with the patient and should also be aware of the nature and capability of the care that will be rendered. The physician should know whether or not the local EMS system can provide defibrillation and other lifesaving care and should also be familiar with the triage strategy for patients with suspected MI.

### **Emergency Medical Services Systems**

Each community prehospital EMS system should develop a plan to triage and provide rapid initial medical care to patients with ischemic-type chest discomfort. In most cities in the United States trained emergency medical technicians (EMTs) work in several different healthcare settings: (1) the emergency medical section of the fire department, (2) hospital-based ambulance systems, and (3) department of health services. To minimize time to treatment, particularly for cardiopulmonary arrest, many systems incorporate professional first responders to provide CPR and defibrillation. Ideally there should be a sufficient number of trained personnel so that a first responder can be at the victim's side within 5 minutes. Public service personnel such as police, firefighters, public works employees, and other first-aid providers have frequently been trained successfully as first responders. A sense of urgency in managing patients with ischemic-type chest discomfort must be imparted to EMS personnel. Rapid identification and treatment of the acute MI patient is imperative.

Early access to EMS is promoted by a 911 system currently available to 80% of the United States population.<sup>8,9</sup> Enhanced 911 systems provide the caller's location, permitting rapid dispatch of prehospital personnel to locations even if the caller is not capable of verbalizing or the dispatcher cannot understand the location of the emergency. Unfortunately the capabilities of EMS systems vary considerably among communities, some providing little beyond first aid, whereas others have formal, advanced protocols for the management of patients with suspected MI or ischemic-type chest discomfort. The latter offers promise in favorably influencing outcomes in such patients. Because patients with acute MI are at relatively high risk of sudden death during the first hour after onset of symptoms, a prehospital EMS system that can provide defibril-

**Table 1.** Chest Pain Checklist for Use by EMT/Paramedic for Diagnosis of Acute Myocardial Infarction and Thrombolytic Therapy Screening

Check each finding below. If all [yes] boxes are checked, and ECG indicates ST elevation or new BBB, reperfusion therapy with thrombolysis or primary PTCA may be indicated. Thrombolysis is generally not indicated unless all [no] boxes are checked and BP  $\leq$ 180/110 mm Hg.

	Yes	No
Ongoing chest discomfort ( $\geq$ 20 min and $<$ 12 h)	<input type="checkbox"/>	—
Oriented, can cooperate	<input type="checkbox"/>	—
Age $>$ 35 y ( $>$ 40 if female)	<input type="checkbox"/>	—
History of stroke or TIA	—	<input type="checkbox"/>
Known bleeding disorder	—	<input type="checkbox"/>
Active internal bleeding in past 2 weeks	—	<input type="checkbox"/>
Surgery or trauma in past 2 weeks	—	<input type="checkbox"/>
Terminal illness	—	<input type="checkbox"/>
Jaundice, hepatitis, kidney failure	—	<input type="checkbox"/>
Use of anticoagulants	—	<input type="checkbox"/>
 Systolic/diastolic blood pressure		
Right arm: ____ / ____		
Left arm: ____ / ____		
 ECG done	Yes	No
High-risk profile*	<input type="checkbox"/>	—
Heart rate $\geq$ 100 bpm	<input type="checkbox"/>	—
BP $\leq$ 100 mm Hg	<input type="checkbox"/>	—
Pulmonary edema (rales greater than one half way up)	<input type="checkbox"/>	—
Shock	<input type="checkbox"/>	—
*Transport to hospital capable of angiography and revascularization if needed.		
Pain began	—	AM/PM
Arrival time	—	AM/PM
Begin transport	—	AM/PM
Hospital arrival	—	AM/PM

EMT indicates emergency medical technician; ECG, electrocardiogram; BBB, bundle branch block; PTCA, percutaneous transluminal coronary angioplasty; BP, blood pressure; TIA, transient ischemic attack. Adapted from the Seattle/King County EMS Medical Record.

lation is mandatory.<sup>8,14</sup> The survival of patients who develop ischemia-induced ventricular fibrillation (VF) depends on rapid deployment of defibrillation. The survival rate of prehospital treatment for all patients with cardiac arrest (those with and without acute MI) varies from 1% to 25%.<sup>15-19</sup> If VF occurs under observation and immediate defibrillation is successful, almost all such patients survive and recover completely.<sup>20</sup> Therefore, the AHA has recommended that every ambulance that transports cardiac arrest victims should be equipped with a defibrillator.<sup>21</sup> However, this goal is yet to be realized.

Automated external defibrillators (AEDs) have been shown to be effective and safe.<sup>18,19,21-23</sup> They can be used by first responders with a minimum of training to quickly and accurately analyze rhythms and deliver defibrillation shocks to patients in VF. Systems that incorporate AEDs to shorten response times are highly desirable. Prehospital providers trained and capable of providing ACLS with drugs, intubation, and other therapy further improve the patient's chances for survival.

Undirected prehospital assessments of patients with ischemic-type chest discomfort can lead to excessive evaluation times and can impede rapid delivery of appropriate therapy.<sup>24</sup> Procedures need to be in place for each EMS system so that a targeted history, physical examination, prehospital ECG, and initial treatment take place in 20 minutes or less. Recently, highly skilled prehospital healthcare providers have been trained and equipped to evaluate patients with ischemic-type chest discomfort by using a checklist and performing 12-lead ECGs in the prehospital setting (Table 1). The checklist should be designed to determine the likelihood of MI and the presence or absence of comorbid conditions and underlying conditions in which thrombolytic therapy may be hazardous. The checklist should facilitate detection of patients with suspected MI who are at especially high risk, including those with tachycardia ( $\geq$ 100 bpm), hypotension ( $\leq$ 100 mm Hg), or signs of shock or pulmonary edema. If available, prehospital ECGs should be obtained in all patients with ischemic-type chest discomfort and transmitted to the ED physician for interpretation and instructions. Such advances accelerate the initial diagnosis and administration of thrombolytic agents after the patient's arrival in the ED.<sup>5,25,26</sup> Active involvement of local healthcare providers—particularly cardiologists and emergency physicians—is needed to formulate local EMS protocols for patients with suspected MI, provide training, and secure equipment. Virtually all states have regulations and standards for emergency personnel, training, and equipment. It is useful for those involved in the emergency care of patients with acute MI to be familiar with these regulations.

### Prehospital-Initiated Thrombolysis

Randomized controlled trials of fibrinolytic therapy have demonstrated the benefit of initiating thrombolytic therapy as early as possible after onset of ischemic-type chest discomfort.<sup>27-29</sup> It seems rational therefore to expect that if thrombolytic therapy could be started at the time of prehospital evaluation, a greater number of lives could be saved. The value of reducing delay until treatment depends not only on the amount of time saved but when it occurs. Available data suggest that time saved within the first 1 to 2 hours has greater biological importance than time saved during the later stages of acute MI.<sup>5,7,27,28,30</sup> Several randomized trials of prehospital-initiated thrombolysis have advanced our understanding of the impact of early treatment.<sup>5,31-34</sup> Acquisition of ECGs in the field and use of a chest-pain checklist (Table 1) leads to more rapid prehospital and hospital care.<sup>5,26</sup> Although none of the individual trials showed a reduction in mortality with prehospital-initiated thrombolytic therapy, a meta-analysis of all available trials demonstrated a 17% relative improvement in outcome associated with prehospital therapy (95% confidence interval [CI], 2% to 29%).<sup>34</sup> The greatest improvement in outcome is observed when treatment can be initiated in the field 60 to 90 minutes earlier than in the hospital.<sup>5,33-35</sup>

Although prehospital-initiated thrombolytic therapy results in earlier treatment, the time savings can be offset in most cases by an improved hospital triage with resultant "door-to-

"needle time" reduced to 30 minutes or less.<sup>4</sup> However, only a small percentage (5% to 10%) of patients with chest pain in the prehospital setting have acute MI and are eligible for thrombolytic therapy.<sup>5,25,36</sup> Ensuring proper selection of patients for therapy can be difficult, and avoiding therapy when it is contraindicated has important medical, legal, and economic implications. For these reasons, a general national policy of prehospital thrombolytic therapy cannot currently be advocated. However, in special settings in which physicians are present in the ambulance or prehospital transport times are 90 minutes or longer, this therapeutic strategy should be considered. Observations from prehospital trials suggest that prehospital systems should focus on early diagnosis (a relatively minor augmentation in prehospital services) instead of delivery of therapy.

### III. Initial Recognition and Management in the Emergency Department

#### Recommendation

##### *Class I*

1. Emergency department acute MI protocol that yields a targeted clinical examination and a 12-lead ECG within 10 minutes and a door-to-needle time that is less than 30 minutes.

#### *Detection/Quantification and Risk Assessment*

Physicians evaluating patients in the ED for possible admission to the coronary care unit (CCU) face the difficult task of avoiding unnecessary admissions but also minimizing the number of patients discharged home inappropriately. Certain subgroups of patients are known to present with unusual symptoms of acute MI. Women often experience atypical ischemic-type chest discomfort,<sup>37</sup> while the elderly may complain of shortness of breath more frequently than ischemic-type chest discomfort.<sup>25</sup> In addition, with the advent of reperfusion therapy and the desire to minimize door-to-needle time for administration of thrombolytic agents or rapid triage to the catheterization laboratory for primary PTCA, there is a clear need for better methods of prompt identification of patients experiencing a true acute MI as accurately and as soon as possible. The ECG and a history of ischemic-type chest discomfort remain the primary methods for screening patients for myocardial ischemia and infarction. The 12-lead ECG in the ED is at the center of the decision pathway because of the strong evidence that ST-segment elevation identifies patients who benefit from reperfusion therapy. In patients with ischemic-type chest discomfort, ST-segment elevation on the ECG has a specificity of 91% and a sensitivity of 46% for diagnosing acute MI.<sup>38</sup> Mortality increases with the number of ECG leads showing ST elevation.<sup>39</sup> Current data do not support administration of thrombolytic agents to patients without ST elevation or BBB, and the benefit of primary PTCA remains uncertain in this population. However, it remains

important to admit such patients to the hospital for medical therapy and possible cardiac catheterization (Fig 1).

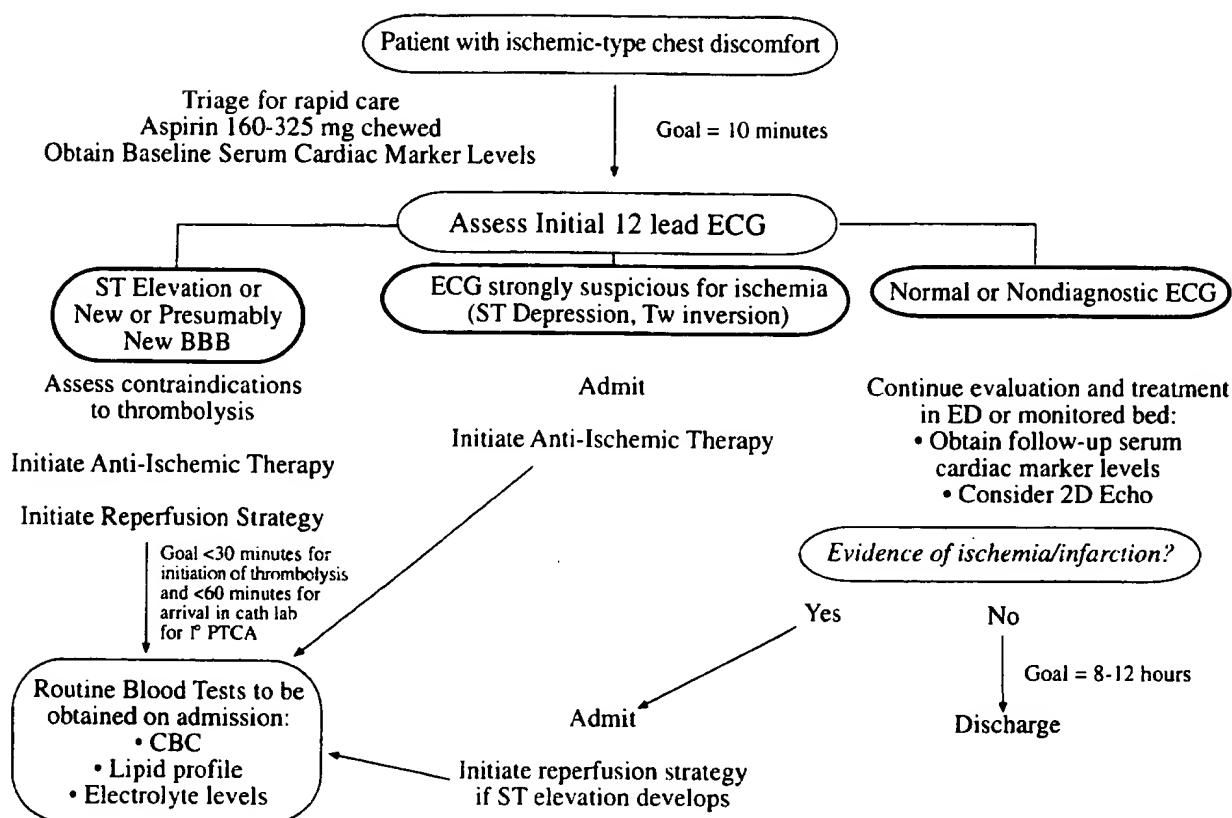
Initial errors in ECG interpretation can result in up to 12% of patients being categorized inappropriately (ST elevation versus no elevation), demonstrating a potential benefit of accurate computer-interpreted electrocardiography and facsimile transmission to an expert. Other decision aids such as high-risk clinical indicators,<sup>40,41</sup> rapid determination of cardiac serum markers,<sup>42,43</sup> two-dimensional echocardiographic screening for regional wall motion abnormalities,<sup>44</sup> myocardial perfusion imaging,<sup>45</sup> and computer-based diagnostic aids<sup>46,47</sup> are of greatest importance in patients in whom the ECG is nondiagnostic. Two-dimensional echocardiography (trans-thoracic and transesophageal) is of particular value for rapid triage decisions in patients suspected of having an aortic dissection. Because lethal ventricular arrhythmias may develop abruptly in patients with an acute coronary syndrome, all patients should be monitored electrocardiographically on arrival in the ED. It is important to examine serial tracings during evaluation in the ED for development of ST elevation, an event that may be detected by intermittent visual inspection of the oscilloscope or auditory alarms in systems with continuous ST-monitoring capability.

All patients with complicated infarctions (eg, cardiogenic shock) and/or those requiring sophisticated, labor-intensive treatments (eg, intra-aortic balloon counterpulsation) should be admitted to the CCU. In many hospitals physicians admit low-risk MI patients to a coronary observation unit or telemetry unit where electrocardiographic monitoring and defibrillation equipment are available, but other forms of monitoring are not, and staffing is reduced.

According to the World Health Organization (WHO) definition, the diagnosis of MI is based on the presence of at least two of the following three criteria: (1) a clinical history of ischemic-type chest discomfort, (2) changes on serially obtained electrocardiographic tracings, and (3) a rise and fall in serum cardiac markers.<sup>10,48</sup> Approximately 70% to 80% of patients with MI present with ischemic-type chest discomfort.<sup>49,50</sup> Conversely, less than 25% of patients admitted to the hospital with ischemic-type chest discomfort are subsequently diagnosed as having had an acute MI.<sup>51,52</sup> Although ST-segment elevation and/or Q waves on the ECG are highly indicative of MI, about 50% of patients with MI do not exhibit ST elevation<sup>53</sup> but display other or nondiagnostic ECG changes.<sup>54</sup> Thus, for the majority of patients, the laboratory plays an essential role in establishing the diagnosis of MI (Fig 2).

An ideal serum marker of MI should be present early and in high concentration in the myocardium and should be absent from nonmyocardial tissue and serum.<sup>55,56</sup> It should be rapidly released into the blood after myocardial injury, and there should be a stoichiometric relation between the plasma level of the marker and the extent of myocardial injury. The marker should persist in blood for a sufficient length of time to provide a convenient diagnostic time window. Finally, measurement should be easy, inexpensive, and rapid.<sup>57</sup>

Creatine kinase-MB (CK-MB) is the current standard



laboratory test for confirmation of MI, although it is by no means perfect.<sup>55-57</sup> Its drawbacks include lack of specificity for cardiac muscle, resulting in false-positive results and inability to detect MI with sufficient sensitivity in the first 6 to 8 hours.<sup>55,58</sup> There is also uncertainty regarding the meaning of increased levels of CK-MB in the presence of normal total CK levels. In addition, CK-MB is excreted rapidly and usually does not remain elevated in the blood more than 72 hours.<sup>56</sup>

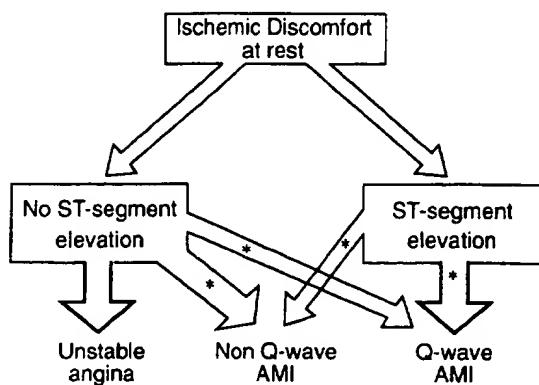
CK-MB exists in only one form in myocardial tissue but in different isoforms (or subforms) in the plasma. An absolute level of CK-MB<sub>2</sub> greater than 1 U/L or a ratio of CK-MB<sub>2</sub> to CK-MB<sub>1</sub> of 1.5 has improved sensitivity and specificity for diagnosis of MI within the first 6 hours as compared with conventional assays for CK-MB.<sup>59</sup> Cardiac specific troponin T (cTnT) and I (cTnI) are new markers for acute MI.<sup>58,60,61</sup> Rapid whole blood bedside assays are now available, and increases in serum levels of cTnT and cTnI may therefore occur relatively early after muscle damage and may be present for several days after MI (up to 7 days for cTnI and up to 10 to 14 days for cTnT).<sup>61</sup> An elevated cTnT level (greater than 0.1 ng/mL) on admission in a patient with an acute coronary syndrome is an important indicator of subsequent cardiac events.<sup>62,63</sup>

Myoglobin, a low molecular weight heme protein found in cardiac and skeletal muscle, is released more rapidly from infarcted myocardium than CK-MB but is also excreted rapidly by renal clearance. Although myoglobin elevations may be seen as early as 2 hours after infarction, the lack of cardiac specificity suggests a need for confirmation of the cardiac

**Figure 1.** Algorithm for management of patients with suspected acute myocardial infarction in the emergency department (ED). All patients with ischemic-type chest discomfort should be evaluated rapidly and receive aspirin. The initial 12-lead electrocardiogram (ECG) is used to define the acute management strategy. Patients with ST-segment elevation or new or presumably new bundle branch block (BBB) should be considered candidates for reperfusion; those without ST-segment elevation but with an ECG and clinical history that are strongly suspicious for ischemia should be admitted for initiation of anti-ischemic therapy (see Fig 4). Patients with a normal or nondiagnostic ECG should undergo further evaluation in the ED or short-term observation until results of serial serum cardiac marker levels are obtained. The following routine blood tests should be obtained in all patients admitted: a complete blood count (CBC), lipid profile, and electrolyte levels. Tw indicates T wave; PTCA, percutaneous transluminal coronary angioplasty. Adapted from Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald EB, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 1996. Philadelphia, Pa: WB Saunders.

source of myoglobin by supplementary tests such as CK-MB or cardiac specific troponin (Table 2).<sup>64,65</sup>

Assays for biochemical markers of myocardial necrosis must be interpreted in the context of the time-dependent process of MI. Some markers may be more efficient at detecting MI in patients presenting early (eg, myoglobin), while others are useful for detecting patients who present late (eg, cardiac specific troponin T and troponin I). A major difficulty in interpreting the results of clinical trials with biochemical markers is the lack of a



**Figure 2.** Nomenclature of acute coronary syndromes. Patients with ischemic discomfort may present with or without ST-segment elevation on the electrocardiogram. The majority (large arrow) of patients with ST-segment elevation ultimately develop a Q wave acute myocardial infarction (AMI), while a minority (small arrow) develop a non-Q wave AMI. Of patients who present without ST-segment elevation, the majority (large arrows) are ultimately diagnosed as either unstable angina or non-Q wave AMI based on the presence or absence of a cardiac marker such as CK-MB detected in the serum; a minority of such patients ultimately develop a Q wave AMI. The spectrum of clinical conditions ranging from unstable angina to non-Q wave AMI and Q wave AMI is referred to as acute coronary syndromes. \*Positive serum cardiac marker. Adapted from Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald EB, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*, 1996, Philadelphia, Pa: WB Saunders.

clear gold standard. The WHO criteria are inadequate for many cases of MI, especially when CK and CK-MB values are only minimally elevated above the normal range.

### Routine Measures (Oxygen, Nitroglycerin, Aspirin)

#### Recommendations

##### Class I

- Supplemental oxygen, intravenous access, and continuous electrocardiographic monitoring should be established in all patients with acute ischemic-type chest discomfort.
- An ECG should be obtained and interpreted within 10 minutes of arrival in the ED in all patients with suspected acute ischemic-type chest discomfort.

Although the specific diagnosis of acute MI can be made with absolute certainty only occasionally at the time of a patient's entry into the healthcare system, the immediate management of all acute coronary syndromes is generally the same. All patients suspected of having an acute MI should have a clinical and electrocardiographic evaluation that is prompt and targeted to estimate the likelihood that the presenting condition is an acute MI as opposed to one of its potentially lethal mimics: aortic dissection, acute pericarditis, acute myocarditis, spontaneous pneumothorax, or pulmonary embolism.

Although local settings vary widely, the entry process should be completed by a health team member (or members) with the competency to make such an assessment within a very short time of the patient's presentation, ideally within the first 10 minutes and certainly no more than 20 minutes from presentation. Only then should specific procedures or therapies be given, except for securing peripheral venous access. At this entry stage it is important that all members of the healthcare team interact with the patient and family in a warm and caring fashion while projecting professionalism and confidence.

#### Oxygen

#### Recommendations

##### Class I

- Overt pulmonary congestion.
- Arterial oxygen desaturation ( $\text{SaO}_2$  less than 90%).

##### Class IIa

- Routine administration to all patients with uncomplicated MI during the first 2 to 3 hours.

##### Class IIb

- Routine administration of supplemental oxygen to patients with uncomplicated MI beyond 3 to 6 hours.

It has become universal practice to administer oxygen, usually by nasal prongs, to virtually all patients suspected of having acute ischemic-type chest discomfort, although it is not known whether this therapy limits myocardial damage or reduces morbidity or mortality. If oxygen saturation monitoring is used, therapy with supplemental oxygen is indicated if the saturation is less than 90%. Experimental results indicate that breathing oxygen may limit ischemic myocardial injury.<sup>66</sup>

**Table 2.** Serum Markers of Acute Myocardial Infarction

	Cardiac Troponins			
	Myoglobin	cTnI	cTnT	CK-MB
Molecular weight (kD)	17	23	33	86
First detectable (h)	1-2	2-4	3-4	2-4
100% sensitivity (h)	4-8	8-12	8-12	6-10
Peak (h)	4-8	10-24	10-24	6-12
Duration (d)	(0.5-1.0)	5-10	5-14	2-4
				0.5-1.0

cTnI indicates cardiac specific troponin I; cTnT, cardiac specific troponin T. Adapted with permission from Adams J, Abendschein D, Jaffe A. Biochemical markers of myocardial injury: is MB creatine kinase the choice for the 1990s? *Circulation*. 1993;88:750-763.

and there is evidence oxygen administration reduces ST-segment elevation in patients with MI as well.<sup>67</sup> The rationale for use of oxygen is based on the observation that even with uncomplicated MI, some patients are modestly hypoxic initially, presumably because of ventilation-perfusion mismatch and excessive lung water.<sup>68</sup>

In patients with severe CHF, pulmonary edema, or a mechanical complication of acute MI, significant hypoxemia may not be corrected with supplemental oxygen alone. Continuous positive-pressure breathing or endotracheal intubation and mechanical ventilation are often required in such cases and should not be unnecessarily delayed.<sup>69</sup> A variety of mechanical ventilators are available, and multiple modes are possible. For patients who do not have a depressed sensorium and are capable of initiating spontaneous ventilation, the preferred modes to use include intermittent mandatory ventilation, assist control, or pressure-support ventilation.<sup>70</sup>

For patients without complications, it should be recalled that excess administration of oxygen can lead to systemic vasoconstriction, and high flow rates can be harmful to patients with chronic obstructive airway disease. On the other hand, because administration of nitroglycerin dilates the pulmonary vascular bed and increases ventilation-perfusion abnormalities, it is reasonable to provide supplemental oxygen, at least in the initial hours, for all patients suspected of having an acute MI. In the absence of compelling evidence for established benefit in uncomplicated cases and in view of its expense, there appears to be little justification for continuing its routine use beyond 2 to 3 hours.

### Nitroglycerin

#### Recommendations for Intravenous Nitroglycerin

##### *Class I*

1. For the first 24 to 48 hours in patients with acute MI and CHF, large anterior infarction, persistent ischemia, or hypertension.

2. Continued use (beyond 48 hours) in patients with recurrent angina or persistent pulmonary congestion.

##### *Class IIa*

None.

##### *Class IIb*

1. For the first 24 to 48 hours in all patients with acute MI who do not have hypotension, bradycardia, or tachycardia.

2. Continued use (beyond 48 hours)\* in patients with a large or complicated infarction.

##### *Class III*

1. Patients with systolic pressure less than 90 mm Hg or severe bradycardia (less than 50 bpm).

Considering that the use of nitrates in acute MI was believed to be contraindicated until the early 1970s,<sup>71</sup> it is

rather striking that today, with the exception of hypotensive patients, virtually all patients with acute ischemic syndromes will receive at least 1 sublingual nitroglycerin tablet before admission to the hospital. Aside from its known clinical benefit in alleviating ischemic myocardial pain, nitroglycerin is now appreciated as having a dilatory effect on the vascular smooth muscle in vessels throughout the body. Thus, vasodilation of the coronary arteries themselves (especially at or adjacent to sites of recent plaque disruption), the peripheral arteries, and the venous capacitance vessels is particularly beneficial to the patient with acute infarction. However, inadvertent systemic hypotension with resulting worsening of myocardial ischemia is the most serious potential complication of nitroglycerin therapy. Thus, patients with ischemic-type chest discomfort should receive sublingual nitroglycerin unless the initial systolic blood pressure is less than 90 mm Hg. It should be avoided in the presence of marked bradycardia (less than 50 bpm) or tachycardia<sup>72</sup> and used with extreme caution, if at all, in patients with suspected right ventricular infarction. Patients with right ventricular infarction are especially dependent on adequate right ventricular preload to maintain cardiac output and can experience profound hypotension during administration of nitrates.<sup>73</sup>

Long-acting oral nitrate preparations should be avoided in the early management of acute MI. Sublingual or transdermal nitroglycerin can be used, but intravenous infusion of nitroglycerin allows for more precise minute-to-minute control of this agent. Intravenous nitroglycerin can be successfully titrated by frequent measurement of cuff blood pressure and heart rate. Although invasive hemodynamic monitoring is not mandatory, it may be preferable if high doses of vasodilating agents are required, blood pressure instability ensues, or there is clinical doubt about the adequacy of LV filling pressure. Although quite effective in relieving ischemic-type chest discomfort due to acute coronary syndromes, nitroglycerin should not be used as a substitute for narcotic analgesia that is usually required to manage pain associated with acute MI. For a detailed discussion of the pharmacotherapy and relevant clinical studies pertaining to the use of nitroglycerin in acute MI, see "Rationale and Approach to Pharmacotherapy."

### Analgesia

The clinical observation of rapid and complete relief of pain after early reperfusion with thrombolytic therapy reinforces the concept that the pain of acute MI is due to continuing ischemia of viable but jeopardized myocardium rather than the effects of completed myocardial necrosis. Efforts to control pain therefore may reasonably involve use of anti-ischemic interventions, including, in addition to reperfusion, oxygen, nitrates,  $\beta$ -adrenoceptor blocking agents, and, in some circumstances, intra-aortic balloon counterpulsation. Effective analgesia (eg, intravenous morphine) should be administered promptly at the time of diagnosis and should not be delayed on the premise that to do so will obscure ability to evaluate the results of anti-ischemic therapy. See "Hospital Management" for more detailed discussion of proper analgesia.

\*Oral or topical preparations may be substituted.

**Aspirin****Recommendations****Class I**

1. A dose of 160 to 325 mg should be given on day 1 of acute MI and continued indefinitely on a daily basis thereafter.

**Class IIb**

1. Other antiplatelet agents such as dipyridamole or ticlopidine may be substituted if true aspirin allergy is present.

The Second International Study of Infarct Survival (ISIS-2) has shown conclusively the efficacy of aspirin alone for treatment of evolving acute MI with a 35-day mortality reduction of 23%.<sup>29</sup> When combined with streptokinase, the reduction in mortality was 42%. A meta-analysis demonstrated that aspirin reduced coronary reocclusion and recurrent ischemic events after thrombolytic therapy with either streptokinase or alteplase.<sup>74</sup> In a dose of 160 mg or more, aspirin produces a rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A<sub>2</sub> production. Accordingly, aspirin now forms part of the early management of all patients with suspected acute MI and should be given promptly and certainly within the first 24 hours at a dose between 160 and 325 mg and continued daily indefinitely.

Unlike fibrinolytic agents, there is little evidence for a time-dependent effect of aspirin on early mortality. However, data do support the contention that a chewable aspirin is absorbed more quickly than one swallowed in the early hours after infarction, particularly after opiate therapy. The use of aspirin is contraindicated in those with a hypersensitivity to salicylate and should be used with caution in patients with active ulcer disease. Aspirin suppositories (325 mg) can be used safely and are the recommended route of administration for patients with severe nausea and vomiting or known upper-gastrointestinal disorders. There is currently no evidence that other antiplatelet agents such as dipyridamole, ticlopidine, or sulfipyrazone have any advantage over aspirin for mortality reduction after acute MI. See "Rationale and Approach to Pharmacotherapy" for additional discussion on the use of aspirin in the management of acute MI, and "Preparation for Discharge From the Hospital."

**Atropine****Recommendations**

The following recommendations are applicable from early after onset of acute MI to 6 or 8 hours afterward:

**Class I**

1. Sinus bradycardia with evidence of low cardiac output and peripheral hypoperfusion or frequent premature ventricular complexes at onset of symptoms of acute MI.
2. Acute inferior infarction with type I second- or third-degree atrioventricular (AV) block associated with symptoms of hypotension, ischemic discomfort, or ventricular arrhythmias.
3. Sustained bradycardia and hypotension after administration of nitroglycerin.

4. For nausea and vomiting associated with administration of morphine.

**5. Ventricular asystole.****Class IIa**

1. Symptomatic patients with inferior infarction and type I second- or third-degree heart block at the level of the AV node (ie, with narrow QRS complex or with known existing BBB).

**Class IIb**

1. Administration concomitant with (before or after) administration of morphine in the presence of sinus bradycardia.
2. Asymptomatic patients with inferior infarction and type I second-degree heart block or third-degree heart block at the level of the AV node.
3. Second- or third-degree AV block of uncertain mechanism when pacing is not available.

**Class III**

1. Sinus bradycardia greater than 40 bpm without signs or symptoms of hypoperfusion or frequent premature ventricular contractions.

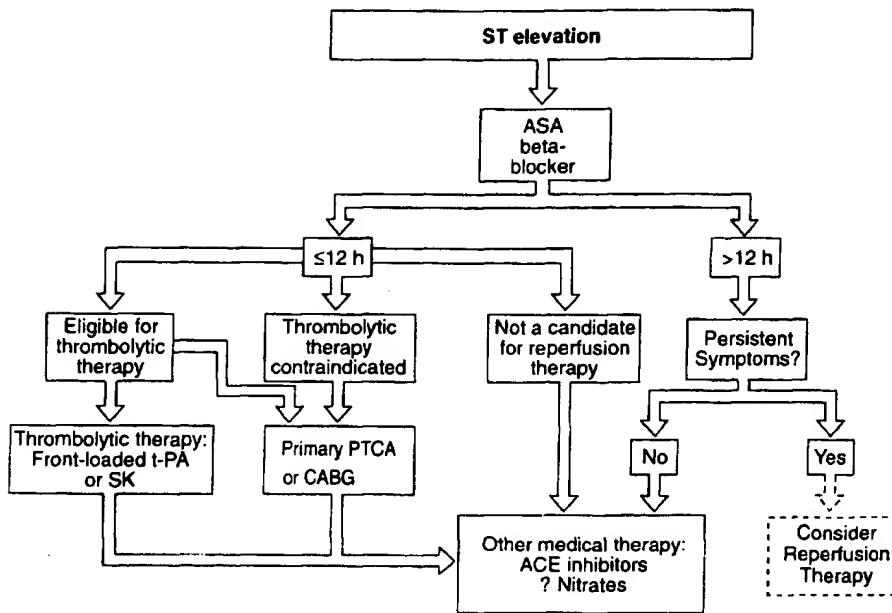
2. Type II AV block and third-degree AV block and third-degree AV block with new wide QRS complex presumed due to acute MI.

By its parasympatholytic (anticholinergic) activity, atropine sulfate reduces vagal tone, enhances the rate of discharge of the sinus node, and facilitates AV conduction.<sup>75</sup> It may be given as an adjunct to morphine administration when nausea and vomiting occur. During the early moments to hours of acute ischemia or acute MI, atropine is particularly useful in treating sinus bradycardia associated with reduced cardiac output and signs of peripheral hypoperfusion, including arterial hypotension, confusion, faintness, or frequent premature ventricular complexes.<sup>76</sup> In this setting, leg elevation and intravenous administration of atropine may be lifesaving.

***Atropine for Atrioventricular Block, Sinus Bradycardia, or Ventricular Asystole***

Atropine is the drug of choice for the occasional treatment of type I second-degree AV block, especially when complicating inferior MI. It is occasionally useful in third-degree AV block at the AV node level in either restoring AV conduction or enhancing the junctional response. When AV block or sinus bradycardia is associated with CHF, hypotension, or frequent and complex ventricular arrhythmias, atropine may improve AV conduction, increase the sinus rate, and avoid the need for immediate insertion of a transvenous pacemaker.<sup>77</sup> As a rule, however, in the absence of hemodynamic compromise, treatment of sinus bradycardia or first- or second-degree AV block is not indicated. Similarly, atropine is rarely, if ever, the drug of choice for management of type II second-degree AV block. On occasion, while failing to improve AV block, atropine may increase the sinus rate, and, in fact, enhance the block.

The recommended dosage of atropine for bradycardia is 0.5 to 1.0 mg intravenously (IV), repeated if needed every 3 to 5 minutes to a total dose of no more than 2.5 mg (0.03 to



0.04 mg/kg), the amount that produces complete vagal blockade. Atropine may also be therapeutic in ventricular asystole, for which the recommended dose is 1 mg IV, to be repeated every 3 to 5 minutes (while CPR continues) if asystole persists. The total cumulative dose should not exceed 2.5 mg over 2.5 hours. The peak action of atropine given intravenously is observed within 3 minutes.<sup>1</sup>

#### Side Effects

When administered in doses of less than 0.5 mg or other than intravenously, atropine may produce a paradoxical effect (namely, bradycardia and depression of AV conduction),<sup>78</sup> which is due either to central reflex stimulation of the vagus or a peripheral parasympathomimetic effect on the heart. Urinary retention is not uncommon following administration of atropine and can be deleterious to the patient with acute MI. Repeated administration of atropine may produce adverse central nervous system effects, including hallucinations and fever. Careful dosing and observation after administration of atropine is necessary because the sinus tachycardia that follows may increase ischemia. Rarely, ventricular tachycardia and fibrillation occur after intravenous administration of atropine.<sup>79</sup>

Pacing is the treatment of choice for symptomatic bradycardia not responding promptly to atropine administration.

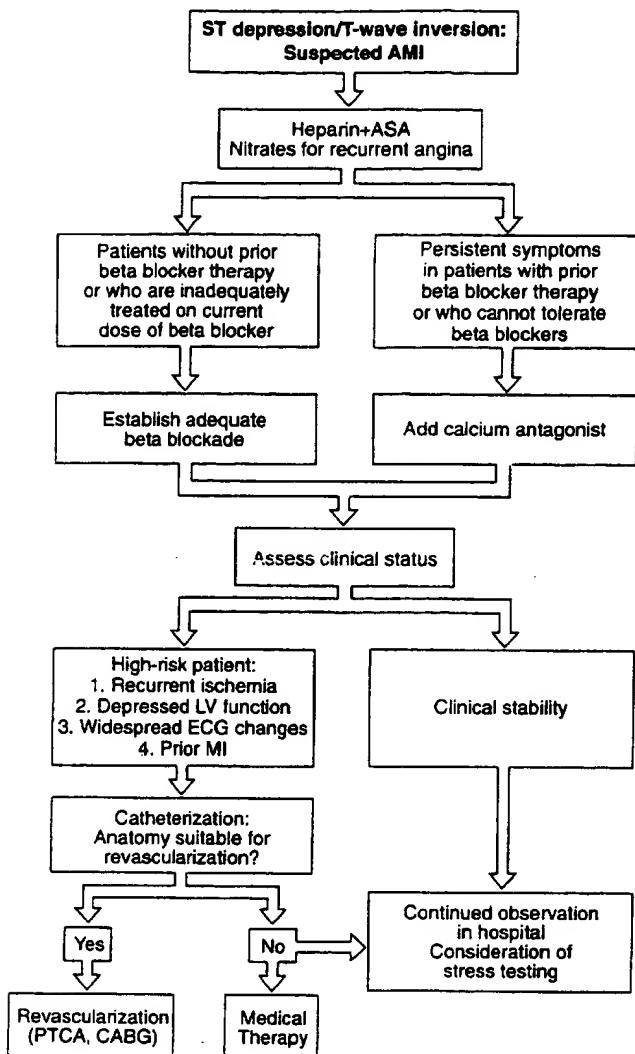
#### Risk Stratification and Management of ST-Segment Elevation/Bundle Branch Block Cohort

#### Newer Concepts

The spectrum of myocardial ischemia consists of patients with clinical presentations that cover the following range of diagnoses: stable angina, unstable angina, MI without ST elevation, and MI with ST elevation. Clinical discrimination among unstable angina, Q wave, and non-Q wave MI can only

**Figure 3.** Recommendations for management of patients with ST elevation. All patients with ST-segment elevation on the electrocardiogram should receive aspirin (ASA),  $\beta$ -adrenoceptor blockers (in the absence of contraindications), and an antithrombin (particularly if tissue-type plasminogen activator [t-PA] is used for thrombolytic therapy). Whether heparin is required in patients receiving streptokinase (SK) remains a matter of controversy; the small additional risk for intracranial hemorrhage may not be offset by the survival benefit afforded by adding heparin to SK therapy. Patients treated within 12 hours who are eligible for thrombolytics should expeditiously receive either frontloaded TPA or SK or be considered for primary percutaneous transluminal coronary angioplasty (PTCA). Primary PTCA is also to be considered when thrombolytic therapy is absolutely contraindicated. Coronary artery bypass graft (CABG) may be considered if the patient is less than 6 hours from onset of symptoms. Individuals treated after 12 hours should receive the initial medical therapy noted above and, on an individual basis, may be candidates for reperfusion therapy or angiotensin-converting enzyme (ACE) inhibitors (particularly if left ventricular function is impaired). Modified from Antman EM. Medical therapy for acute coronary syndromes: an overview. In: Califf RM, ed. *Atlas of Heart Diseases*, VIII. Philadelphia, Pa: Current Medicine; 1996.

be made retrospectively after serial ECGs and serum cardiac markers have been obtained (Fig 2). Patients with ST-segment elevation have a high likelihood of a coronary thrombus occluding the infarct-related artery.<sup>80,81</sup> However, not every ST-elevation MI evolves into a Q wave MI. Angiographic evidence of occlusive coronary thrombus formation may be seen in more than 90% of patients with ST-elevation MI but in only 1% of patients with stable angina and about 35% to 75% of patients with unstable angina or non-Q wave MI.<sup>80-83</sup> Commonly indicated treatment regimens for all acute coronary ischemic syndromes include aspirin, heparin,  $\beta$ -adrenoceptor blockers, and nitrates. Thrombolytic therapy is highly effective in patients with ST elevation or presumably new LBBB (which obscures the electrocardiographic diagnosis of MI)<sup>27</sup> (Fig 3).



**Figure 4.** Recommendations for management of patients with acute myocardial infarction (MI) without ST elevation. All patients without ST elevation should be treated with an antithrombin and aspirin (ASA). Nitrates should be administered for recurrent episodes of angina. Adequate  $\beta$ -adrenoceptor blockade should then be established; when this is not possible or contraindications exist, a calcium antagonist can be considered. High-risk patients should be triaged to cardiac catheterization with plans for revascularization if they are clinically suitable; patients who are clinically stable can be treated more conservatively, with continued observation in the hospital and consideration of a stress test to screen for myocardial ischemia that can be provoked. LV indicates left ventricular; ECG, electrocardiographic; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft. Modified from Antman EM. Medical therapy for acute coronary syndromes: an overview. In: Califf RM, ed. *Atlas of Heart Diseases, VIII*. Philadelphia, Pa: Current Medicine; 1996.

At the same time, evidence now suggests that thrombolytic therapy is ineffective (for normal or nonspecific electrocardiographic presentations) and possibly even harmful (for ST-depression presentation) in unstable angina and non-ST-elevation MI subgroups.<sup>27,84</sup> Fig 4 presents a suggested schema for management of acute MI without ST-segment elevation.

## Noninvasive Imaging in the Emergency Department

Screening patients who present with ischemic-type chest discomfort in the ED is an area of clinical and economic importance. Because only 25% or less of patients admitted to the hospital to "rule out" MI actually suffer an MI, accurate screening techniques to identify patients with ongoing necrosis is an important goal. The usefulness of echocardiography in the ED as a means of screening for MI has been validated, but small areas of infarction can be missed, and the age of a regional wall motion abnormality cannot be determined.<sup>85-87a</sup> Thallium and sestamibi imaging in the ED are both very good radioisotope screening techniques<sup>85,88,89</sup> and appear to be quite sensitive. However, their use in the ED is still viewed as experimental and is not recommended. In time, the value of noninvasive imaging may further diminish as rapid assays of specific, earlier, and more sensitive serum markers of myocardial necrosis are developed.<sup>56,58,60,61</sup>

## Thrombolysis

### Recommendations

The constellation of clinical features that must be present (although not necessarily at the same time) to serve as standard indications for administration of thrombolytic therapy to patients with acute MI are as follows: (selection of specific thrombolytic agents or regimens is discussed in "Rationale and Approach to Pharmacotherapy.")

#### Class I

1. ST elevation (greater than 0.1 mV, two or more contiguous leads),\* time to therapy 12 hours or less,<sup>†</sup> age less than 75 years.

2. Bundle branch block (obscuring ST-segment analysis) and history suggesting acute MI.

**Comment:** Treatment benefit is present regardless of gender, presence of diabetes, blood pressure (if less than 180 mm Hg systolic), heart rate, or history of previous MI.<sup>27</sup> Benefit is greater in the setting of anterior MI, diabetes, low blood pressure (less than 100 mm Hg systolic), or high heart rate (greater than 100 bpm). The earlier therapy begins, the better the outcome, with the greatest benefit decidedly occurring when therapy is given within the first 3 hours; proven benefit occurs, however, up to at least within 12 hours of the onset of symptoms. Benefit is less with inferior acute MI, except for the subgroup with associated right ventricular infarction (ST elevation RV-4) or anterior-segment depression.

#### Class IIa

1. ST elevation,\* age 75 years or older.

**Comment:** In persons older than 75 years, the overall risk of mortality from infarction is high without and with therapy. Although the proportionate reduction in mortality is less than in patients younger than 75, the absolute reduction results in 10 lives

\*Repeat ECGs recommended during medical observation in suggestive clinical settings when initial ECG is nondiagnostic of ST elevation.

†Time of symptom onset is defined as the beginning of continuous, persistent discomfort that brought the patient to the hospital.

saved per 1000 patients treated in those over 75. The relative benefit of therapy is reduced.<sup>27</sup>

### Class IIb

1. ST elevation,\* time to therapy greater than 12 to 24 hours.<sup>†</sup>

2. Blood pressure on presentation greater than 180 mm Hg systolic and/or greater than 110 mm Hg diastolic associated with high-risk MI.

**Comment:** Generally there is only a small trend for benefit of therapy after a delay of more than 12 to 24 hours, but thrombolysis may be considered for selected patients with ongoing ischemic pain and extensive ST elevation. Risk of ICH is greater when presenting blood pressure is greater than 180/110 mm Hg, and in this situation the potential benefit of therapy must be weighed carefully against the risk of hemorrhagic stroke. Risk of cardiac rupture appeared to increase with prolonged time to therapy in an earlier meta-analysis<sup>90</sup> but was not associated with increased risk of rupture in a later, larger study.<sup>91</sup> Generally patients presenting more than 12 hours after symptom onset were excluded from some but not all trials. An attempt to lower blood pressure first (with nitrates,  $\beta$ -adrenoceptor blockers, etc) is recommended but is not of proven benefit in lowering the risk of ICH. Primary PTCA or CABG may be considered if available.

### Class III

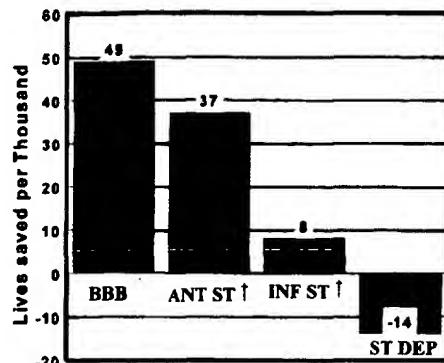
1. ST elevation,\* time to therapy greater than 24 hours,<sup>†</sup> ischemic pain resolved.

2. ST-segment depression only.

**Comment:** In the absence of ST elevation, there is no evidence of benefit for patients with normal electrocardiographic or non-specific changes, and, using current thrombolytic regimens, there is some suggestion of harm (including increased bleeding risk) for patients with ST-segment depression only.<sup>27,92</sup> When marked ST-segment depression is confined to leads V<sub>1</sub> through V<sub>4</sub>, there is a likelihood that this reflects a posterior current of injury and suggests a circumflex artery occlusion for which thrombolytic therapy would be considered appropriate. Very recent retrospective analysis of the Late Assessment of Thrombolytic Efficacy (LATE) Trial<sup>93,94</sup> also casts some uncertainties about withholding thrombolytic therapy from this heterogeneous group of patients.

A collaborative overview from nine trials of thrombolytic therapy (versus control) for acute MI has shown a highly significant ( $P < 0.00001$ ) 18% proportional reduction in 35-day mortality (9.6% fibrinolysis versus 11.5% control) corresponding to a reduction of 18 deaths per 1000 patients treated when data from all patient groups are pooled.<sup>27</sup> In patients with ST elevation, a proportional mortality reduction of 21% occurred. It is now known that this survival benefit can be maintained long term (6 months to at least 4 years).<sup>27,95</sup>

Fig 5 summarizes the number of lives saved per 1000



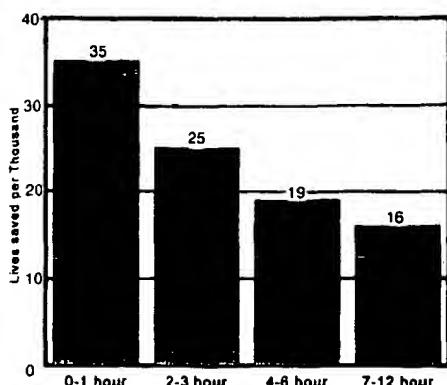
**Figure 5.** Effect of thrombolytic therapy on mortality according to admission electrocardiogram. Patients with bundle branch block (BBB) and anterior ST-segment elevation (ANT ST↑) derive the most benefit from thrombolytic therapy. Effects in patients with inferior ST-segment elevation (INF ST↑) are much less, while patients with ST-segment depression (ST DEP) do not benefit. Adapted from Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-322. Reprinted from *Management of Acute Myocardial Infarction* (Julian D, Braunwald E, eds). Martin GV, Kennedy JW. Choice of thrombolytic agent, p 90, 1994, by permission of the publisher, WB Saunders Co Ltd, London.

patients treated based on the presenting ECG pattern.<sup>96</sup> In general, thrombolytic agents should be administered only to patients with ST-segment elevation greater than 0.1 mV or presumably new LBBB on the ECG.<sup>27,97</sup> However, in the very early phase of acute infarction, giant, hyperacute T waves may be present with no ST-segment elevation. Similarly, direct posterior infarction can result in ST-segment depressions in leads V<sub>1</sub> through V<sub>4</sub>, and in both situations it is appropriate to administer thrombolytic therapy. Thus, it should be clear that certain cases require experienced interpretation of the ECG before withholding reperfusion therapy. Unquestionably, patients with LBBB and anterior ST elevation are at greater inherent risk from MI but also achieve greater benefit with thrombolytic therapy. Although one study<sup>98</sup> suggested that the amount of ST elevation might also predict greater inherent risk and therefore greater benefit, it did not take into account the increased amount of ST elevation seen in patients with anterior infarction. Other factors such as collateral flow<sup>98</sup> clearly influence the amount of ST elevation, which may limit its value for predicting therapeutic benefit.

Additional factors that influence the decision to administer thrombolytic therapy include time since onset of symptoms, patient's age, hemodynamic status, and coexisting medical illnesses (Figs 6 and 7). Myocardial salvage increases with progressively earlier administration of thrombolytic therapy, although a reduction in mortality may still be seen in patients treated up to at least 12 hours from onset of definitive symptoms.<sup>27,99,100</sup> Some patients presenting at more than 12 to 24 hours with persistent ischemic symptoms and ST elevation also may benefit from treatment. Although younger patients

\*Repeat ECGs recommended during medical observation in suggestive clinical settings when initial ECG is nondiagnostic of ST elevation.

†Time of symptom onset is defined as the beginning of continuous, persistent discomfort that brought the patient to the hospital.



**Figure 6.** Effect of thrombolytic therapy on mortality according to time from symptom onset. Patients treated early derive the most benefit. Adapted from Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet Ltd.* 1994;343:311-322. Reprinted from *Management of Acute Myocardial Infarction* (Julian D, Braunwald E, eds). Martin GV, Kennedy JW. Choice of thrombolytic agent, p 90, 1994, by permission of the publisher, WB Saunders Co Ltd, London.

achieve a greater relative reduction in mortality compared with older patients, the increasing absolute mortality rates with advancing age result in progressively greater absolute mortality reductions up to age 75. Benefit may also be achieved after age 75 but is less certain than at younger ages.<sup>27,101</sup> Advanced age does increase risk of stroke after acute MI, both without and with thrombolytic therapy. Given the much greater mortality risk of MI, the elderly should be considered candidates for thrombolytic therapy after careful screening for exclusions. Patients should be considered at higher risk if they have any of the following: female gender, advanced age (greater than 70 years), history of previous infarction, atrial fibrillation, anterior infarction, rales in more than one third of the lung fields, hypotension, and sinus tachycardia or diabetes mellitus.<sup>27,102</sup> Indeed, certain subgroups of patients with an especially high likelihood of benefiting from successful reperfusion include those with hypotension, tachycardia, and a history of diabetes mellitus or prior MI.

Early placebo-controlled trials of thrombolysis for MI raised concern about a paradoxical increase in mortality during the first 24 hours after thrombolysis that was later offset by a greater reduction in mortality in the thrombolytic groups.<sup>27</sup> More recently conducted thrombolytic trials have confirmed a "high density" of mortality in the first 24 hours but suggest that this may be attributed primarily to pump failure from unsuccessful reperfusion rather than an early hazard of thrombolysis.<sup>103</sup>

#### Risk of Stroke

Thrombolytic therapy is associated with a slight but definite excess risk of stroke that occurs predominantly within the first day of therapy.<sup>27</sup> Clinical variables that can be ascertained in the ED that predict an increased risk of ICH are advanced age

(older than 65 years, odds ratio 2.2, 95% CI, 1.4 to 3.5), low body weight\* (less than 70 kg, odds ratio 2.1, CI 1.3 to 3.2), hypertension on presentation (odds ratio 2.0, CI 1.2 to 3.2), and use of alteplase (odds ratio 1.6, CI 1.0 to 2.5).<sup>104-106</sup> The number of risk factors at presentation may be used to estimate the probability of ICH and is shown in Fig 8.\* Although no firm guidelines have been established, ICH rates less than 1% have generally been regarded as acceptable in clinical trials, considering the overall favorable benefit-risk profiles, whereas rates greater than 1.5% or higher have been viewed as unacceptable high.<sup>107</sup>

#### Net Clinical Benefit

Clinicians must carefully weigh the risk-benefit ratio of thrombolysis for individual patients. Hesitancy to prescribe thrombolytic therapy arises from concern about intracranial bleeding and uncertainty about eligibility criteria. The generally higher mortality rate among MI patients who do not undergo thrombolysis underscores the need for heightened awareness of current indications for thrombolysis through such projects as the NHAAP.<sup>108</sup> Decision analysis methods suggest that appropriate use of thrombolytic therapy in eligible patients would save many additional lives annually in the United States.<sup>109</sup>

#### Contraindications/Cautions

Hemorrhage represents the most important risk of thrombolytic therapy, especially ICH, which may be fatal in one half to two thirds of patients. Contraindications and cautions to thrombolytic use are given in Table 3.

#### Summary of Initial Diagnostic and Treatment Strategy

A summary of initial diagnostic and treatment strategies for patients with acute MI with ST elevation or BBB, focusing on emergency management, is provided in Table 4.

#### Primary Percutaneous Transluminal Coronary Angioplasty

##### Recommendations

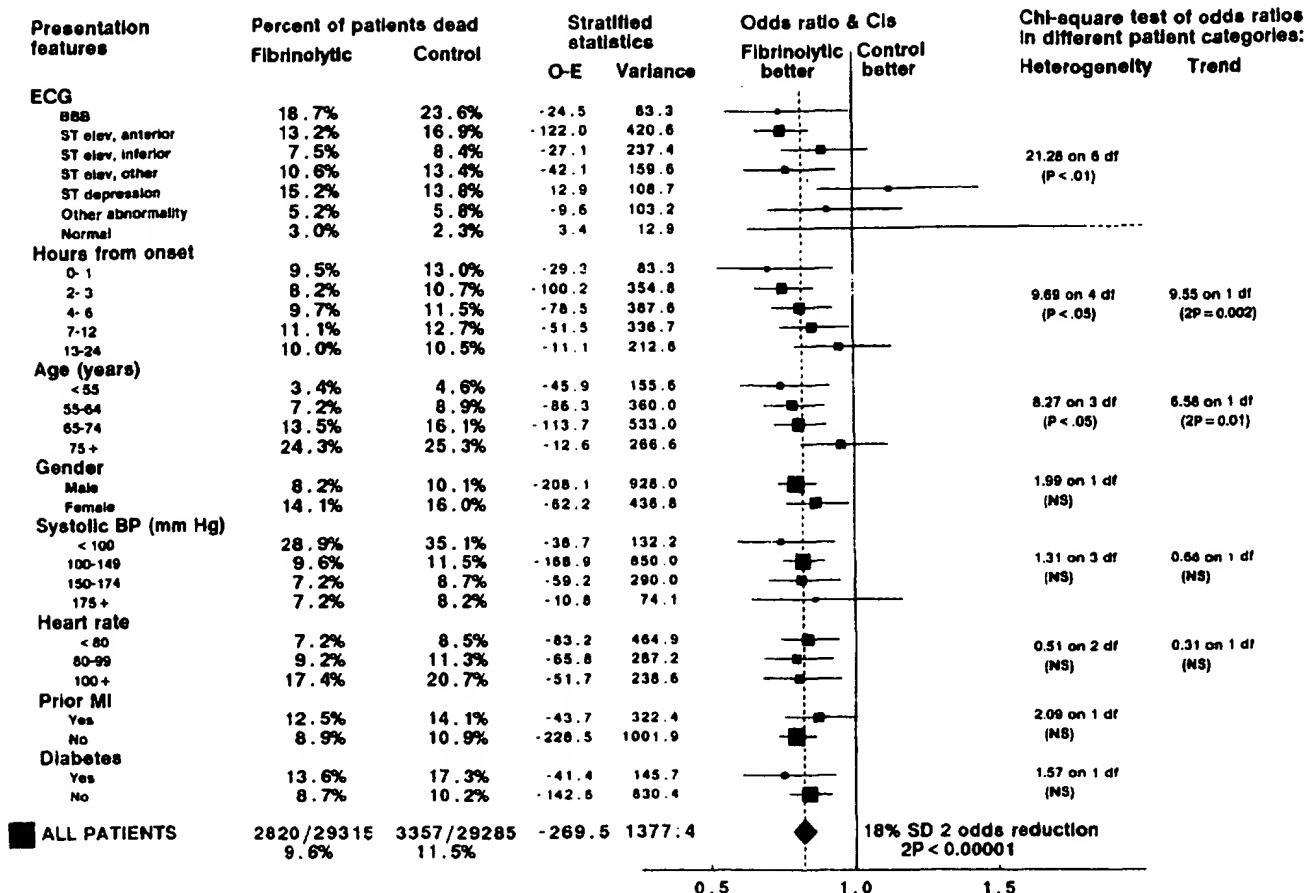
##### Class I

- As an alternative to thrombolytic therapy only if performed in a timely fashion by individuals skilled in the procedure† and supported by experienced personnel in high-volume centers.‡

\*To reduce risk, the dose of 90-minute alteplase should be adjusted downward for low body weight (less than 67 kg). Similarly, the 180-minute regimen should be adjusted downward for patients who weigh less than 65 kg.

†Individuals who perform more than 75 PTCA procedures per year.<sup>110</sup>

‡Centers that perform more than 200 PTCA procedures per year.<sup>110</sup>



### Class IIa

- As a reperfusion strategy in patients who are candidates for reperfusion but who have a risk of bleeding contraindication to thrombolytic therapy (Table 3).
- Patients in cardiogenic shock.

### Class IIb

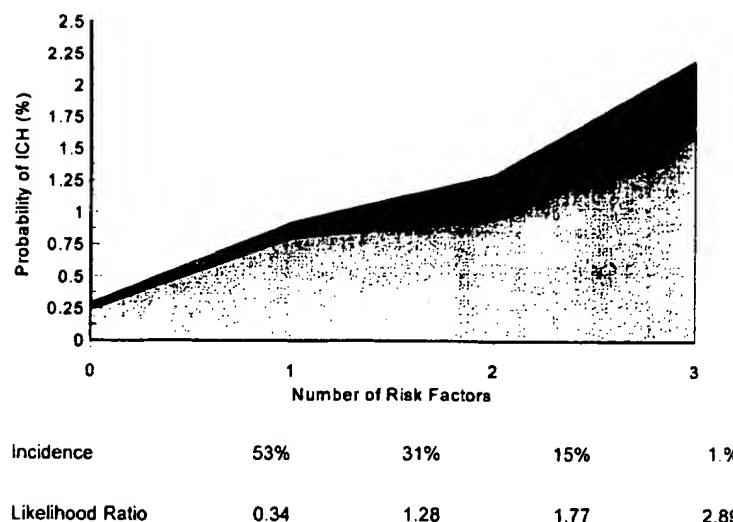
- As a reperfusion strategy in patients who fail to qualify for thrombolytic therapy for reasons other than a risk of bleeding contraindication.

**Comment:** There is serious concern that a routine policy of primary PTCA for patients with acute MI will result in unacceptable delays in achieving reperfusion in a substantial number of cases and less than optimal outcomes if performed by less experienced operators. Strict performance criteria must be mandated for primary angioplasty programs so that such delays in revascularization and performance by low-volume operators/centers do not occur. Interventional cardiologists and centers must operate within a specified "corridor of outcomes" to include (1) balloon dilation within 60 to 90 minutes of diagnosis of acute MI; (2) a documented clinical success rate with Thrombolysis in Myocardial Infarction (TIMI) II through III flow attained in more than 90% of patients without emergency CABG, stroke, or death; (3) emergency CABG rate less than 5% among all patients undergoing the procedure; (4) actual performance of angioplasty in a high percentage of patients (85%) brought to the laboratory;

Figure 7. Mortality differences during days 0 through 35 subdivided by presentation features in a collaborative overview of results from nine trials of thrombolytic therapy. At center absolute mortality rates are shown for fibrinolytic and control groups for each clinical feature at presentation listed at left. The odds ratio of death in fibrinolytic group to that in control group is shown for each subdivision (black square) along with 95% confidence interval (horizontal line). The summary odds ratio at bottom corresponds to an 18% proportional reduction in 35-day mortality and is highly statistically significant. This translates to a reduction of 18 deaths per 1000 patients treated with thrombolytic agents. O-E indicates observed versus expected ratio; CIs, confidence intervals; ECG, electrocardiogram; BBB, bundle branch block; ST elev, ST-segment elevation; df, degrees of freedom; BP, blood pressure; MI, myocardial infarction; SD, standard deviation. Adapted from Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet Ltd.* 1994;343:311-322. Reprinted from *Management of Acute Myocardial Infarction* (Julian D, Braunwald E, eds). Antman EM. General hospital management, pp 42-44, 1994, by permission of the publisher, WB Saunders Co Ltd, London.

and (5) mortality rate less than 12%. Otherwise, the focus of treatment should be the early use of thrombolytic therapy.

Since publication of the original report of primary (direct) PTCA as an alternative to thrombolytic therapy in patients with acute MI,<sup>111</sup> its merits have been debated.<sup>112,113</sup> There are



**Figure 8.** Risk of intracranial hemorrhage (ICH) during thrombolytic therapy. At bottom is estimated incidence of frequency of one or more of the following risk factors: age >65 y, weight <70 kg, hypertension on admission, and use of tissue plasminogen activator (TPA) in patients with acute MI who are potential candidates for thrombolytic therapy. The likelihood ratio describes the probability of finding the risk profile among patients with intracranial bleeding divided by the probability of finding the same risk profile among patients without intracranial bleeding. Curves depict estimated probability of ICH assuming an overall incidence of 0.5% and 0.75% (bottom and top curves respectively). Adapted from data in Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial hemorrhage during thrombolytic therapy. *Lancet* 1993; 342:1523-1528.

no randomized controlled trials of primary PTCA versus no reperfusion. Thus, the recommendations are based on findings from small and moderately sized comparative trials of primary PTCA and thrombolysis and from indirect evidence.

Initial assessments showed that PTCA restored antegrade flow in the occluded infarct-related artery in more than 90% of patients and was associated with a 1-year survival rate of 90% to 96%.<sup>114-117</sup> Subsequently several randomized trials compared PTCA and thrombolytic therapy in patients with acute MI.<sup>118-120</sup> In these studies PTCA was reported to successfully restore antegrade coronary flow in approximately 88% to 95%

of attempts. In the study of Zijlstra et al,<sup>118</sup> follow-up angiography weeks after infarction showed that the infarct-related artery was patent in 91% of those who had primary PTCA and in 68% of those who received streptokinase ( $P=.001$ ), and the residual infarct-related artery stenosis was less in those who underwent PTCA. Those in whom primary PTCA was performed also had fewer in-hospital adverse events (nonfatal reinfarction or death) and were less likely to have recurrent ischemia or to require coronary revascularization over the period of follow-up.

**Table 3.** Contraindications and Cautions for Thrombolytic Use in Myocardial Infarction\*

Contraindications	
• Previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 year	
• Known intracranial neoplasm	
• Active internal bleeding (does not include menses)	
• Suspected aortic dissection	
Cautions/relative contraindications	
• Severe uncontrolled hypertension on presentation (blood pressure >180/110 mm Hg) <sup>†</sup>	
• History of prior cerebrovascular accident or known intracerebral pathology not covered in contraindications	
• Current use of anticoagulants in therapeutic doses (INR ≥2-3); known bleeding diathesis	
• Recent trauma (within 2-4 weeks), including head trauma or traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)	
• Noncompressible vascular punctures	
• Recent (within 2-4 weeks) internal bleeding	
• For streptokinase/anistreplase: prior exposure (especially within 5 d-2 y) or prior allergic reaction	
• Pregnancy	
• Active peptic ulcer	
• History of chronic severe hypertension	

\*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive. <sup>†</sup>Could be an absolute contraindication in low-risk patients with myocardial infarction (see text).

**Table 4.** Diagnostic and Treatment Measures in Patients With ST Elevation or Bundle Branch Block

Initial diagnostic measures	
1. Use continuous ECG, automated BP, HR monitoring	
2. Take targeted history (for AMI inclusions, thrombolysis exclusions), check vital signs, perform focused examination	
3. Start IV(s), draw blood for serum cardiac markers, hematology, chemistry, lipid profile	
4. Obtain 12-lead ECG	
5. Obtain chest x-ray (preferably upright)	
General treatment measures	
1. Aspirin, 160-325 mg (chew and swallow)	
2. Nitroglycerin, sublingual: test for Prinzmetal's angina, reversible spasm; anti-ischemic, antihypertensive effects	
3. Oxygen: sparse data; probably indicated, first 2-3 h in all; continue if low arterial oxygen saturation (<90%).	
4. Adequate analgesia: small doses of morphine (2-4 mg) as needed	
Specific treatment measures	
1. Reperfusion therapy: goal—door-to-needle time <30 min; door-to-dilatation time <60 min	
2. Conjunctive antithrombotics: aspirin, heparin (especially with TPA)	
3. Adjunctive therapies: $\beta$ -adrenoceptor blockade if eligible, intravenous nitroglycerin (for anti-ischemic or antihypertensive effects), ACE inhibitor (especially with large or anterior AMI, heart failure without hypotension [SBP >100 mm Hg], previous MI).	

ECG indicates electrocardiogram; BP, blood pressure; HR, heart rate; AMI, acute myocardial infarction; IVs, intravenous administrations; TPA, tissue plasminogen activator; ACE, angiotensin converting enzyme; SBP, systolic blood pressure.

Similarly, Gibbons et al<sup>119</sup> found that those who underwent primary PTCA were less likely to require coronary revascularization for recurrent ischemia over a 6-month follow-up period than those treated with alteplase. In this study the two groups had similar myocardial salvage (the primary end point), LV ejection fraction, incidence of recurrent MI, and survival. The Primary Angioplasty in Myocardial Infarction (PAMI) Investigators<sup>120</sup> found a significant difference in their primary end point (combined death and nonfatal reinfarction) between patients receiving PTCA (5.1%) or alteplase (12.0%,  $P = .02$ ) but no significant differences in LV function or mortality. In a post hoc analysis of high-risk patients (ie, older than 70 years, with anterior infarction or tachycardia on presentation), mortality was only 2% for those who had primary PTCA and 10% for those who received thrombolysis ( $P=.01$ ). The survival benefit of PTCA was at least partly due to the fact that those who received thrombolytic therapy had an excessive incidence of cerebrovascular hemorrhage with death; in fact, cardiac-related deaths were similar in the two groups.

A meta-analysis suggests that, in comparison with thrombolytic therapy, primary PTCA reduces the incidence of subsequent hospital morbidity, readmission, and follow-up costs largely by reducing recurrent ischemia following intervention.<sup>121</sup> However, this benefit comes at the cost of performing PTCA on all patients presenting with infarction (rather than the 20% to 40% who require revascularization for clinical indications following thrombolytic therapy in these trials).<sup>118-120</sup>

Before considering PTCA as the preferred therapy for acute MI, several caveats should be kept in mind. Because only about 20% of hospitals in the United States have cardiac catheterization laboratories and even less have the capability of performing emergency PTCA, its applicability as a primary therapy for acute MI is limited. Although transfer of the patient with MI to a facility that can perform PTCA is possible, the necessary time delay in achieving reperfusion may outweigh any added benefit.

The excellent results attained in the limited number of patients studied in the randomized trials to date can be attributed to several factors, including (1) the extensive experience of these investigators in performing PTCA in the setting of acute MI; (2) their enthusiastic commitment to all details of the protocol; (3) the resulting dedication of their institutions and support personnel to the project; and (4) the capability to perform PTCA within a short time frame (by 60 to 90 minutes of arrival at hospital). These important considerations may not be reproducible in the community setting and for all acute MI patients not enrolled in specific protocols. For example, there are now several reports from community-based registries in both the United States and Europe showing a greater time delay to primary PTCA (door-to-balloon inflation) compared with thrombolytic therapy (door-to-needle).<sup>122-126</sup> In these registries in-hospital mortality of patients treated with primary angioplasty ranged from 5% to 10% and was similar to that of patients treated with thrombolysis at the same hospitals.

In the recently completed GUSTO-IIb trial results pre-

sented at the 45th Annual Scientific Session of the American College of Cardiology, held in Orlando, Fla, in March 1996, 1138 patients were randomly selected to receive either direct angioplasty or thrombolytic therapy with accelerated alteplase.<sup>127</sup> Although the mortality (5.7% versus 7.0%) and the composite of death, reinfarction, and disabling stroke (9.6% versus 13.1%) showed a trend toward favoring direct angioplasty, the magnitude of the effect was less than that observed in the previous small trials, and the cost of each therapy was within several hundred dollars of the other. It is also important to recognize that the results of the randomized trials were achieved only in patients who were eligible for thrombolytic therapy, and the findings do not necessarily apply to persons who are not eligible. In addition, 2% to 5% of patients initially referred for PTCA will require emergency CABG surgery, either because the artery is not suitable for PTCA or failed angioplasty requires further surgical intervention. Accordingly, primary PTCA should be performed in centers with cardiac surgical capability or in those institutions with a proven plan for rapid access to cardiac surgery in a nearby facility.

#### **Recommendations for Early Coronary Angiography in the ST-Segment Elevation or Bundle Branch Block Cohort Not Undergoing Primary Percutaneous Transluminal Coronary Angioplasty**

##### **Class I**

- None.

##### **Class IIa**

- 1. Patients with cardiogenic shock or persistent hemodynamic instability.

##### **Class IIb**

- 1. Patients with evolving large or anterior infarcts treated with thrombolytic agents in whom it is believed that the artery is not patent and adjuvant PTCA is planned.

##### **Class III**

- 1. Routine use of angiography and subsequent PTCA within 24 hours of administration of thrombolytic agents.

#### **Recommendations for Emergency or Urgent Coronary Artery Bypass Graft Surgery**

##### **Class I**

- 1. Failed angioplasty with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery.

- 2. Acute MI with persistent or recurrent ischemia refractory to medical therapy in patients with coronary anatomy suitable for surgery who are not candidates for catheter intervention.

- 3. At the time of surgical repair of postinfarction VSD or mitral valve insufficiency.

##### **Class IIa**

- 1. Cardiogenic shock with coronary anatomy suitable for surgery.

**Class IIb**

1. Failed PTCA and small area of myocardium at risk; hemodynamically stable.

**Class III**

1. When the expected surgical mortality rate equals or exceeds the mortality rate associated with appropriate medical therapy.

**Comment:** These recommendations are supplementary to those published recently in a more complete set of general guidelines and indications for CABG by another ACC/AHA subcommittee<sup>128</sup> and are restricted in general to patients with acute MI and associated complications. The basis for recommending surgery in emergency circumstances is based on the documented benefits of CABG for severe multivessel disease or left main coronary artery stenosis, particularly with reduced LV function,<sup>128-131</sup> with the realization that risk of emergency CABG is greater than that for elective operation.

Previous studies<sup>132-134</sup> suggested that emergency CABG improved survival and salvaged more myocardium than matched retrospective control groups developed before the widespread use of thrombolytic therapy and primary PTCA. More recently, emergency CABG has been used for acute MI patients when other interventional therapies have failed or have not been indicated.

### Risk Stratification and Management in Non-ST-Segment Elevation Cohort

#### Recommendations for Early Coronary Angiography and/or Interventional Therapy

**Class I**

1. Patients with recurrent (stuttering) episodes of spontaneous or induced ischemia or evidence of shock, pulmonary congestion, or LV dysfunction.

**Class IIa**

1. Patients with persistent ischemic-type discomfort despite medical therapy and an abnormal ECG or two or more risk factors for coronary artery disease.

2. Patients with chest discomfort, hemodynamic instability, and an abnormal ECG.

**Class IIb**

1. Patients with chest discomfort and an unchanged ECG.
2. Patients with ischemic-type chest discomfort and a normal ECG and more than two risk factors for coronary artery disease.

**Patient Characteristics**

Ischemic-type chest discomfort in the setting of nondiagnostic electrocardiographic findings (no ST elevation) represents a continuum between chronic stable angina and typical acute MI. Unstable angina and MI without ST elevation represent two of the most common cardiac emergencies requiring hospitalization and account for over 650 000 discharges

per year in the United States. While the optimal treatment regimen or strategy for such patients is under investigation, a proposed schema is presented in Fig 4.

It is believed that acute MI accompanied by nondiagnostic ECG changes is related to acute disruption of an atherosclerotic plaque.<sup>82,135-137</sup> Although there are few angiographic and clinical correlations with the syndrome, studies to date have suggested that, unlike MI with ST elevation, total coronary occlusion is much less common.<sup>82,138-140</sup> In the initial study by DeWood et al,<sup>82</sup> total coronary occlusion occurred in only 32% of patients studied early by angiography, a greater than 70% stenosis was present in more than 70%, and a few had normal coronary arteries. When total occlusion is present, it most commonly occurs in the circumflex distribution, which is electrocardiographically silent, or in a vessel that is well collateralized.<sup>82,141</sup>

The earlier descriptions of MI patient populations often differ from more contemporary descriptions. Patients with suspected MI are best classified in terms of the initial electrocardiographic finding: ST-segment elevation and BBB versus other electrocardiographic findings at the time of ischemic-type chest discomfort and admission. Earlier studies of non-Q wave MI described a heterogeneous population that included patients with both ST-segment elevation and nondiagnostic electrocardiographic abnormalities at the time of presentation.<sup>142</sup> Many of these studies showed that patients with non-Q wave infarction had a relatively low in-hospital mortality rate.<sup>143,144</sup> Recurrent ischemia, recurrent MI, and death in the weeks after discharge, however, occurred frequently.<sup>145-148</sup> Findings from more recent registries of consecutive patients with acute MI show that nondiagnostic ECGs at the time of admission are more common in the elderly and those with prior MI.<sup>25,149</sup> One study showed that ST elevation occurred in 54% of patients older than 75 years compared with 63% of patients under 55. Fewer elderly patients were eligible for thrombolytic therapy, and invasive means of reperfusion such as primary PTCA were also performed less frequently in this group.<sup>25</sup> The overall incidence of non-Q wave MI may be increasing with the advancing age of the population and the greater use of thrombolytic therapy, aspirin, and  $\beta$ -adrenoceptor blockers.

Most randomized trials in patients with MI have been conducted in those with ST-segment elevation, although a few early studies were less restrictive and provide some insight into the effect of thrombolysis on outcome in patients with nondiagnostic electrocardiographic changes. In the first GISSI study (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) of streptokinase for acute MI, no benefit was associated with thrombolytic therapy in patients with ST-segment depression at the time of admission. Mortality rates in patients with ST-segment depression were in fact higher in those treated with streptokinase (20.5% versus 16.2% in the control group).<sup>28</sup> Patients with less abnormal or undefined electrocardiographic abnormalities had a lower overall mortality rate, averaging about 8%. Again, there was no treatment benefit of thrombolytic therapy.<sup>28</sup> It is important to

realize, however, that only about 10% of all patients randomly assigned in the trial had nondiagnostic electrocardiographic findings. Thus, they likely represent a very select group of patients with nondiagnostic electrocardiographic changes who were deemed eligible and appropriate for thrombolytic therapy. In the ISIS-2 trial there was a relatively high mortality rate in patients with MI and ST-segment depression and no treatment benefit from thrombolytic therapy.<sup>29</sup> In patients with MI who had only T-wave abnormalities, mortality rates were low (about 5%); in patients with normal ECGs, the mortality rate was 1% to 2%. In a recent overview of the early, large randomized placebo-controlled trials of thrombolytic therapy, 3.6% of the entire group had ST-segment depression.<sup>27</sup> The mortality rate for those receiving thrombolysis was 15.2%, compared with 13.8% for control subjects, a higher rate than in those with ST elevation. Furthermore, two randomized trials of thrombolytic therapy in patients with unstable angina or MI with nondiagnostic electrocardiographic findings showed no benefit of alteplase compared with treatment with aspirin and heparin alone.<sup>92,150</sup> In summary, the available data do not support the routine use of thrombolytic therapy as a form of reperfusion in patients admitted with ischemic-type chest discomfort and nondiagnostic ECGs.

It should be recognized that relatively few patients with nondiagnostic electrocardiographic findings have been studied to date, and the possibility of benefit, particularly in some subsets of patients, cannot be excluded on the basis of the available data. In the retrospective subgroup analysis of patients enrolled in the LATE study,<sup>93</sup> 1-year mortality was significantly reduced by alteplase in patients presenting initially with ST depression greater than 2 mm (20.1% versus 31.9%,  $P=.006$ ). Thus, although the available data do not support the routine use of thrombolytic therapy in patients with ischemic-type chest discomfort and nondiagnostic ECGs, future prospective trials are warranted to better define the role of thrombolytic therapy in such patients.<sup>94</sup>

Although few patients with nondiagnostic electrocardiographic findings have been treated in trials, it is important to realize that this presentation is not unusual. It was estimated in one consecutive series of patients that almost half of patients with MI were ineligible for acute reperfusion because of a nondiagnostic ECG at the time of admission, yet the mortality rate for this subset was high (14%).<sup>84,151</sup>

### Pharmacological Therapy in Patients in the Non-ST-Segment Elevation Cohort

Despite the recent realization that at least half of patients with enzymatic evidence of myocardial necrosis do not have ST-segment elevation on the ECG, little is known about the specific response of these patients to pharmacological therapy other than their lack of mortality reduction with thrombolytic therapy as discussed above. On presentation these patients cannot be distinguished from those with unstable angina without myocardial necrosis. The initial pharmacological therapy, other than avoidance of thrombolytic therapy, is the same

as for all patients with unstable angina or infarction with ST-segment elevation (Fig 2). It is important to recognize, however, that these recommendations are made in the absence of information specific to this very large group of patients. In patients with recurrent episodes of pain, serial ECGs should be repeated frequently. The development of sustained ST elevation is an indication for thrombolysis or primary PTCA. If the ECG remains nondiagnostic but stuttering symptoms continue, urgent angiography is recommended.

### Interventional Therapy

There is considerable variation in use of acute catheterization, angiography, and catheter or surgical interventions in the management of patients with suspected acute MI and non-diagnostic ECGs. The approach of acute catheterization has been promoted to quickly identify the problem and offer reperfusion therapy and expedite hospital discharge. Although PTCA for non-Q wave MI has been shown to have high success rates and improve myocardial function within the infarct zone, few data exist regarding its effect on clinical outcome.<sup>92,152</sup> To elucidate this issue, the TIMI-IIIB study was undertaken.

TIMI-IIIB was the largest (1473 patients) randomized, controlled trial of early intervention versus a conservative strategy in patients with unstable angina/MI and nondiagnostic electrocardiographic changes.<sup>92</sup> Results showed no significant difference in the primary outcome (death, MI, or a positive exercise test at 42 days) in patients receiving early angiography and revascularization versus the conservative approach (16.2% versus 18.1%),<sup>92</sup> although the trend favored PTCA. Hospital mortality rates in the population selected for this trial were low (less than 3%) and considerably lower than the rate observed for patients with nondiagnostic electrocardiographic changes in the large trials. The rate of death and recurrent MI in patients with documented MI and nondiagnostic ECGs treated by early intervention versus conservative therapy was 7.2% versus 9.9%. Similarly, in the subset of patients with unstable angina, these event rates (7.2% versus 6.9%) were not significantly different. In those with ST-segment depression, death and MI occurred in 10.5% in the early intervention group versus 11.8% in the conservative group. All patients were treated with  $\beta$ -adrenoceptor blockers, calcium channel blockers, nitrates, heparin, and aspirin. By 42 days, 64% of the conservative-treatment group had received coronary angiography because of either spontaneous or induced ischemia on provocative testing. Fifty-five percent of the angiograms were done before hospital discharge. The greatest difference between the two treatment strategies was the need for rehospitalization, which was less in patients undergoing early intervention (7.8% versus 14.1%, respectively.) The initial hospitalization was statistically shorter, but the average time saved was only 15 hours and the lengths of hospital stay were much longer than the national average (10 days). There were no economic comparisons of the two strategies, and thus it is not known whether the cost of routine angiography and

intervention was offset by the reduced need for rehospitalization.

Many physicians in hospitals with full cardiac facilities routinely perform delayed coronary angiography within 2 to 3 days of admission and then revascularization if appropriate, even if the patient remains asymptomatic.<sup>153</sup> Other physicians treat such patients conservatively and perform angiography and revascularization only in those with spontaneous or induced ischemia during provocative testing in the recovery phase of hospitalization. Proponents for the routine use of coronary angiography soon after admission for patients with suspected MI and nondiagnostic electrocardiographic findings argue that (1) a definitive anatomic diagnosis can be made and prognosis can be stratified, based on the extent of coronary disease and LV dysfunction; (2) a therapeutic plan can be executed early in the hospital, possibly reducing length of stay; and (3) patients with critical coronary obstructions can undergo revascularization in the hope that outcome improves and the subsequent need for antianginal medications lessens.<sup>153</sup> However, there are no trials or empiric data substantiating better outcome using this approach. A conservative strategy of risk stratification and a more selective use of procedures may be more cost-effective with revascularization less frequently performed and targeted to those who would most benefit from it.

More recent data from the TIMI-IIIB study<sup>154</sup> suggest that patients with unstable angina or non-Q wave MI who have elevations of cTnI on admission have an increased risk of death or nonfatal MI at 6 weeks. Clearly more studies are needed in this area before a guideline for optimal care can be suggested. In general the outcome of patients with ischemic-type chest discomfort and isolated T wave or other minor abnormalities is favorable, and the relative role of interventions in this group is much less clear.

## IV. Hospital Management

### *Early, General Measures*

#### **Recommendations**

##### **Class I**

1. Selection of electrocardiographic monitoring leads based on infarct location and rhythm.
2. Bed rest with bedside commode privileges for initial 12 hours in hemodynamically stable patients free of ischemic-type chest discomfort.
3. Avoidance of Valsalva.
4. Careful attention to maximum pain relief.

##### **Class IIb**

1. Routine use of anxiolytics.

##### **Class III**

1. Prolonged bed rest (more than 12 to 24 hours) in stable patients without complications.

### **Monitoring for Adverse Events**

Early general measures focus on monitoring for adverse events, preventing such events through protective measures, and treating adverse events when they do occur. Electrocardiographic monitoring is an essential role of CCU staff, who must be adept at rhythm interpretation, lead selection based on infarct location and rhythm,<sup>82</sup> as well as lead placement for detection of right ventricular involvement.<sup>155</sup> Computer algorithms have proved superior to medical personnel for detection of arrhythmias.<sup>156</sup> However, the choice of lead placement and application technique (ie, skin preparation and use of conducting gels) remain essential human skills.

Blood pressure should be measured repeatedly; actual frequency will depend on the severity of the illness. Although invasive arterial monitoring (discussed in "Hospital Management") is preferred in the hypotensive patient, noninvasive monitoring is adequate for most patients. Monitoring with an automatic device that inflates and deflates at programmed intervals is useful, but it must be recognized that measurements may be inaccurate because of inappropriate cuff size or muscle contractions; marked peripheral vasoconstriction can result in falsely low readings. Furthermore, many patients report that the device is irritating and disrupts rest. Pulse oximetry is now routine for continuous monitoring of oxygen saturation and extremely helpful for providing early warning of hypoxemia.

### **Level of Activity**

Protection against adverse events involves a variety of measures aimed at minimizing myocardial damage by maintaining a balance of oxygen supply and demand. If oxygen and aspirin therapy have not been initiated in the ED, they should be administered immediately (see "Initial Recognition and Management in the Emergency Department" for dosing), and the need for nitroglycerin should be determined (see "Rationale and Approach to Pharmacotherapy" for dosing). All healthcare providers should communicate quiet confidence.

Limiting early physical exertion and minimizing sympathetic stimulation (eg, acute ischemic-type chest discomfort and anxiety) are methods of minimizing myocardial oxygen demand that increases the area of myocardial damage when coronary blood flow is limited.<sup>157</sup> In an earlier era the duration of bed rest was extended to several weeks until it was known that prolonged immobility is harmful because of the physiological deconditioning that occurs after even 6 hours in the supine position.<sup>158</sup> Preload decreases because of plasma volume losses that occur early in the bed rest period. Shifts in ventricular filling activate the body's compensatory mechanisms to buffer pressure and volume alterations. Cardiovascular dysfunction after bed rest may be more a function of these fluid shifts than deconditioning from physical inactivity.<sup>159</sup>

A short period (about 12 hours) of bed rest seems prudent for most patients with acute MI with allowances for bedside commode use. Prolonged bed rest is unnecessary except for patients with acute MI who are hemodynamically unstable.

**Table 5.** Sample Admitting Orders

<b>Condition:</b>	Serious
<b>IV:</b>	NS or D <sub>5</sub> W to keep vein open
<b>Vital signs:</b>	q½ h until stable, then q 4 h and p.r.n. Notify if HR <60 or >110; BP <90 or >150; RR <8 or >22. Pulse oximetry x24 h.
<b>Activity:</b>	Bed rest with bedside commode and progress as tolerated after approximately 12 h
<b>Diet:</b>	NPO until pain free, then clear liquids. Progress to a heart-healthy diet (complex carbohydrates=50-55% of kilocalories, monounsaturated and unsaturated fats ≤30% of kilocalories), including foods high in potassium (eg, fruits, vegetables, whole grains, dairy products), magnesium (eg, green leafy vegetables, whole grains, beans, seafood), and fiber (eg, fresh fruits and vegetables, whole-grain breads, cereals).
<b>Medications:</b>	<ul style="list-style-type: none"><li>• Nasal O<sub>2</sub> 2 L/min × 3 h</li><li>• Enteric-coated ASA daily (165 mg)</li><li>• Stool softener daily</li><li>• β-adrenoceptor blockers?</li><li>• Consider need for analgesics, nitroglycerin, anxiolytics</li></ul>

Low-level activities such as toileting, assisted bathing, and light ambulation should be used to prevent physiological deconditioning. Sample admitting orders are presented in Table 5.

“Coronary precautions,” designed to limit physical exertion and sympathetic stimulation, became the standard of care in the 1960s. Iced and hot fluids were restricted as were stimulant beverages, rectal temperature measurements and examinations, and vigorous back rubs; assistance with eating was common, and enforced bed rest was the norm. A recent national survey demonstrates that coronary precautions are still in practice across the United States despite the fact that research does not support their use.<sup>160</sup>

Avoidance of the Valsalva maneuver is the only coronary precaution of universal significance. Forced expiration against a closed glottis causes sudden and intense changes in systolic blood pressure and heart rate. Changes in ventricular loading during the Valsalva maneuver may influence regional endocardial repolarization and predispose the patient to ventricular arrhythmias.<sup>161,162</sup> Age attenuates autonomic cardiovascular responsiveness,<sup>161,163-165</sup> so avoiding use of the Valsalva maneuver may be especially important in persons younger than 45 years. Stool softeners should be prescribed routinely, and a bedside commode rather than a bedpan should be used by all but the most unstable patients.

Blood pressure increases after caffeine intake,<sup>166</sup> but the increase is not clinically significant until 400 mg of caffeine (ie, 2 to 4 cups of coffee, depending on strength and brewing method) is ingested.<sup>167</sup> People who drink caffeinated beverages regularly develop a tolerance after 1 to 4 days,<sup>168,169</sup> regardless of dose. Withdrawal of caffeine is associated with headache<sup>170,171</sup> and increases in heart rate.<sup>172</sup> Routine caffeine drinkers can safely drink several cups of coffee daily even while in the CCU.<sup>173</sup>

### Proper Analgesia (Use of Morphine, Anxiolytics, and the Role of Education)

Patients with acute MI typically exhibit overactivity of the sympathetic nervous system, which adversely increases myocardial oxygen demands through acceleration of heart rate, elevation of arterial pressure, augmentation of cardiac contractility, and a heightened tendency to occurrence of ventricular tachyarrhythmias.<sup>97,174</sup> Because this sympathetic drive arises from a combination of ischemic-type chest discomfort and anxiety, a primary objective of therapy is administration of sufficient doses of an analgesic such as morphine sulfate to relieve what many patients have described as a feeling of impending doom. Morphine sulfate can be administered intravenously at a rate of 2 to 4 mg every 5 minutes, with some patients requiring as much as 25 to 30 mg before pain relief is adequate.<sup>97,175</sup> The current practice of administering morphine in small increments to avoid paradoxical augmentation of sympathetic nervous system tone and respiratory depression may have a tendency to result in too low a cumulative dose being administered. Fear of inducing hypotension also tends to restrict the amount of morphine sulfate administered. It is important to realize that morphine-induced hypotension typically occurs in volume-depleted, orthostatic patients and is not a particular threat to supine patients.<sup>97</sup> It may be more prudent to avoid concomitant use of other vasodilators such as intravenous nitroglycerin in patients with severe unremitting pain. Patients should be instructed to notify the nurse immediately when discomfort occurs and describe its severity using a numeric scale (eg, 1 to 10).

The depressant effect of morphine on ventilation is centrally mediated and widely appreciated. Fortunately, in the setting of acute MI respiratory depression is usually not a significant clinical problem because of the sympathetic discharge associated with severe ischemic-type chest discomfort or pulmonary edema. Administration of 0.4 mg naloxone IV at up to 3-minute intervals to a maximum of 3 doses may be used to relieve morphine-induced respiratory depression, should it occur.

Patient education effectively decreases emotional distress,<sup>176</sup> increases knowledge,<sup>177</sup> and changes behavior<sup>178</sup> following acute MI. Patients want information about risk factors<sup>178</sup> and self-management techniques (eg, how to treat ischemic-type chest discomfort) rather than information about disease pathophysiology (eg, causes of ischemic-type chest discomfort).<sup>179</sup> Effective educational techniques focus on concrete, objective information before procedures are performed.<sup>180</sup> Following are some examples of sensory information that are helpful to patients before they undergo cardiac catheterization:

- “The room will be dimly lit and may feel cool.”
- “You will hear us tell you to take a deep breath and hold it.”
- “The dye will make you feel hot and flushed for about 15 seconds.”

Materials written at a sixth-grade reading level or below are best.<sup>181</sup>

The decreasing length of hospital stays has raised concern about adequate opportunity for appropriate patient education,<sup>182</sup> although short educational sequences have been shown to produce outcomes comparable to lengthy sessions.<sup>178</sup> Innovative presentation styles (eg, programmed instruction, audio-visual techniques, health education television programs) can produce benefits comparable to individual educational sessions.<sup>177,183</sup> All patients may not be ready to learn during hospitalization, and methods of accommodating them until they are ready are greatly needed. Responsibility for some education can be delegated to healthcare professionals who see the patient after discharge (eg, cardiac rehabilitation, home health, or office nurse). Use of a single repository for all educational materials (eg, a binder that travels with the patient) may provide consistency, document material taught, and identify goals that remain. Self-education through personal computer software or videotapes warrants further study. Inclusion of spouses in teaching also increases learning and retention over time.<sup>184</sup>

It is important to note that 80% of all sudden cardiac deaths occur in persons with known cardiovascular disease.<sup>185</sup> Accordingly, family members of acute MI patients should be taught CPR,<sup>186</sup> because most episodes of cardiac arrest occur within 18 months of hospital discharge.<sup>187</sup>

Symptoms of nicotine withdrawal, anxiety, insomnia, depression, difficulty concentrating, irritability, anger, restlessness, and slowed heart rate<sup>188</sup> may occur in hospitalized smokers. Pharmacological therapy can be of benefit to patients experiencing nicotine withdrawal. The proper use of anxiolytics, however, is dependent on a thorough understanding of their pharmacokinetics and pharmacodynamic properties.<sup>29</sup> Agitation and delirium are not uncommon in the CCU, particularly in patients with complicated acute MI and protracted stays in the intensive care setting. In addition, a number of drugs frequently used in the CCU, such as lidocaine, mexiletine, procainamide, atropine, cimetidine, and meperidine, are capable of inducing delirium. Intravenous haloperidol is a rapidly acting neuroleptic that can be given safely and effectively to cardiac patients with agitation. It rarely produces hypotension or requires assisted ventilation. In selected patients the use of anxiolytics may prove beneficial.

Usually, however, routine use of pharmacological anxiolytics is neither necessary nor recommended. Dixon and colleagues<sup>189</sup> have demonstrated that anxiety, blood pressure, heart rate, and ischemic-type chest discomfort were no different in patients treated with diazepam compared with those treated with placebo. Conversely, psychological support provided during hospitalization has been shown to decrease anxiety and depression immediately and for up to 6 months after acute MI.<sup>184</sup> Liberalized visiting rules for patients in critical care can be helpful; several studies have demonstrated no harmful physiological effects attributable to unrestricted visiting policies.<sup>190,191</sup>

### Treatment of Adverse Events

Although the use of prophylactic antiarrhythmic agents in the first 24 hours after MI is not recommended, the availability of atropine, lidocaine, pacing paddles or a pacemaker, a defibrillator, and epinephrine remains prudent for treating important rhythm disorders.\* Lidocaine in a dose of 1.0 to 1.5 mg/kg IV may be used for first-line treatment of sustained ventricular tachycardia (VT) associated with hemodynamic instability. See "Rationale and Approach to Pharmacology" for further recommendations.

Epinephrine plays a prominent role in advanced life support following a circulatory arrest associated with VF, asystole, or electromechanical dissociation.<sup>192</sup> Although it is known to have an adverse effect on cardiac rhythm and increases myocardial oxygen demand, it does support the peripheral vascular tree and thus enhances circulation during external chest compression.

### *Identification and Treatment of the Patient at Low Risk*

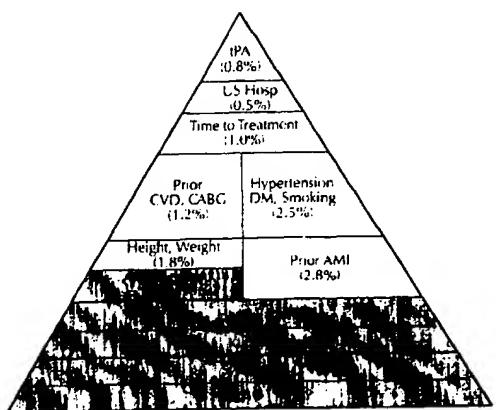
Several methods have been proposed to reduce the cost of caring for acute MI patients: (1) identify true infarcts early; (2) provide early aggressive reperfusion; and (3) streamline the in-hospital phase of management using clinical guidelines and critical pathways, stratifying patients based on risk, and reducing length of CCU stay and total length of stay in hospital.

The ready availability of serum cardiac marker measurements in most hospitals, coupled with significant advances in techniques for rapidly measuring markers that rise into the abnormal range in less than 6 hours (eg, myoglobin,<sup>64,65</sup> CK-MB isoforms,<sup>59</sup> cardiac specific troponin T and I<sup>66,67</sup>) now enable clinicians to diagnose or exclude MI in uncertain cases within 8 to 12 hours from onset of chest discomfort. Use of such rapid biochemical techniques has been shown to reduce length of stay in CCUs, and clinicians are encouraged to assess their current laboratory testing protocols with a goal of more accelerated decision making.<sup>193</sup>

Several reports in the literature suggest that reperfusion protocols with thrombolytic agents or PTCA can significantly reduce hospital stay.<sup>194-197</sup> Important independent predictors of freedom from late major complications include absence of early sustained VT or VF, absence of early sustained hypotension or cardiogenic shock, the presence of only one or two coronary arteries with significant (75%) stenosis, and a preserved LV ejection fraction (greater than 40%).<sup>196</sup>

Using clinical variables at presentation, clinicians can estimate a patient's risk of mortality before administering thrombolytic therapy.<sup>102,198</sup> Although considerable controversy centers around the relative merits of one thrombolytic agent over another, it is important to realize that several clinical variables

\*The committee strongly recommends that physicians and nurses maintain expertise in the correct differentiation of accelerated idioventricular rhythm, bundle branch block, and monomorphic and polymorphic ventricular tachycardia.



**Figure 9.** Influence of clinical characteristics on 30-day mortality after myocardial infarction in patients treated with thrombolytic agents based on experience from the GUSTO (Global Utilization of Streptokinase and TPA for Occluded Arteries) trial. Although considerable attention has been paid to optimizing thrombolytic regimens—indeed, the small absolute differences in mortality observed with different thrombolytic regimens are controversial—it should be emphasized that the choice of the agent is far less important than are certain clinical variables with respect to mortality. This pyramid depicts the importance of such clinical characteristics as calculated from a regression analysis in the GUSTO trial. Numbers in parentheses indicate the proportion of risk of 30-day mortality associated with particular characteristics; shaded blocks indicate variables that constitute 90% of mortality seen in post-MI patients with ST elevation receiving thrombolytic therapy. tPA indicates tissue-type plasminogen activator; US Hosp, patients treated in a US hospital; CVD, cardiovascular disease; CABG, coronary artery bypass graft; DM, diabetes mellitus; AMI, acute myocardial infarction; BP, blood pressure. From Lee KL. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41 021 patients. *Circulation*. 1995;91:1659-1668. Reproduced with permission. Also modified from *Management of Acute Myocardial Infarction* (Julian D, Braunwald E, eds). Antman EM. Medical therapy for acute coronary syndromes: an overview. In: Califf RM, ed. *Acute Myocardial Infarction and Other Acute Ischemic Syndromes*, p 54, 1994, by permission of the publisher, WB Saunders Co Ltd, London.

have a greater influence on a given patient's mortality risk than the exact thrombolytic agent prescribed. A recent analysis from the contemporary reperfusion era provides useful information by summarizing the independent influence of clinical characteristics on 30-day mortality in patients with ST elevation treated with thrombolysis<sup>199</sup> (Fig 9).

#### Triage of Patients With Acute Myocardial Infarction and Other Coronary Syndromes

The premium on cardiac intensive care beds makes it imperative that alternatives to the CCU be developed for patients for whom an MI is excluded and MI patients with a low-risk profile. Persons who are considered at very low risk and who are expected to derive little benefit from thrombolytic therapy (eg, lack of ST-segment displacement on ECG, constellation of clinical features suggesting less impact of thrombolysis on mortality) should nevertheless remain in the hospital to receive other medical interventions, including rest, antiplatelet therapy, antithrombin therapy, and  $\beta$ -adrenoceptor blockers.

Data compiled from multiple studies (largely before the reperfusion era) suggest that patients admitted to the CCU for observation and treatment of suspected MI can be triaged to a low-risk category.<sup>102,200-203</sup> Although extensive data have not been recompiled in this era of reperfusion therapy for MI, clinical experience suggests that patients can be transferred safely out of the CCU as early as 24 to 36 hours after admission if they do not have a history of previous infarction, persistent ischemic pain, CHF, hypotension, heart block, or hemodynamically compromising ventricular arrhythmias. It is unlikely that such patients will require transfer back to the CCU or will die in the hospital.<sup>204</sup>

One of the most important determinants of resource use for management of MI patients is diagnostic testing—an expenditure that may not be necessary in low-risk MI patients and that may prolong hospital stay.<sup>205</sup> Considerable variation exists among countries in management of MI,<sup>206</sup> across and within geographic regions in the United States,<sup>207</sup> across medical specialties,<sup>205</sup> among patients of differing race and gender,<sup>208</sup> and between young and old patients with MI.<sup>209</sup> Even after adjusting for baseline determinants of risk, part of this variation in practice patterns cannot be explained by medical issues, highlighting the need for contemporary guidelines for clinical practice and regular updating of local hospital protocols and critical pathway maps.

Two trends in nursing care have been developed to reduce costs: (1) the use of personnel with less training or without licenses in place of registered nurses and (2) changes in staff-patient ratios. Although patients identified as low risk may be able to be safely managed following such changes, few data are available to document the safety and quality implications of these trends. There is concern that reduction in staffing ratios has not only curtailed time available for in-patient education but has increased the level of stress experienced by critical-care nurses today. Additionally there are data to suggest that alterations in staffing may negatively influence patient recovery rates and treatment success. When mortality rates of hospitals documented to attract high-quality nurses were compared with a matched sample of hospitals that failed to attract such staff, the magnet hospitals had a 4.6% lower mortality rate after adjusting for differences in predicted mortality ( $P=.026$ ).<sup>210</sup> Superior outcomes could not be attributed to patient, organizational, or physician characteristics. Although flexibility in staffing patterns is desirable to respond to the frequent fluctuations in levels of acuity, more data are required before a general recommendation can be made about changes in nurse staffing patterns.

#### Summary of Identification and Treatment of the Patient at Low Risk

Clinicians should strive to identify patients with an acute coronary syndrome who have not sustained an MI ideally within 8 to 12 hours of onset of symptoms. This can be accomplished by serial sampling of serum cardiac markers and use of 12-lead ECGs and their interpretation in the context of the number of hours that have elapsed since onset of the

patient's symptoms rather than adherence to a rigid protocol that requires a specified number of samples be drawn in the hospital. For example, to exclude an MI in a patient presenting to the ED within 4 hours of onset of ischemic-type chest discomfort, blood specimens might be drawn at admission and 8 hours later. A patient presenting 12 hours after onset of discomfort who has a normal ECG and normal serum cardiac marker levels in the ED need not be admitted to the CCU.

The mortality risk of patients who do sustain an MI can be evaluated using an integrated assessment of demographic and clinical variables according to the scheme shown in Fig 9. Low-risk patients include those without a history of previous infarction and who do not experience persistent ischemic pain, CHF, hypotension, heart block, or hemodynamically compromising ventricular arrhythmias. Such patients can be safely transferred out of the CCU within 24 to 36 hours of admission and, provided they remain asymptomatic and without complications, constitute a group of patients who can be considered for early discharge in another 24 to 48 hours.

### *Identification and Treatment of the Patient at High Risk*

#### **Recommendations for Management of Recurrent Chest Discomfort**

##### **Class I**

1. Aspirin for pericarditis.
2.  $\beta$ -Adrenoceptor blockers intravenously, then orally for ischemic-type chest discomfort.
3. (Re)administration of thrombolytic therapy (alteplase) for patients with recurrent ST elevation.
4. Coronary arteriography for ischemic-type chest discomfort recurring after hours to days of initial therapy and associated with objective evidence of ischemia in patients who are candidates for revascularization.

##### **Class IIa**

1. Nitroglycerin intravenously for 24 hours, then topically or orally for ischemic-type chest discomfort.

##### **Class IIb**

1. Corticosteroids for pericarditis.
2. Indomethacin for pericarditis.

#### **Recurrent Chest Pain in the Post-MI Patient:**

##### **Pericarditis and Ischemia**

Recurrent chest pain in the patient still hospitalized after MI requires an evaluation of the cause of the pain while initiating therapy to resolve it, if possible.

The two most common cardiac causes of recurrent chest pain are acute pericarditis and ischemia, with the latter being the more common and potentially more serious. An ECG taken during the recurrent pain and compared with the initial one is clinically helpful.<sup>38</sup> Usually, recurrent pain within the first 12 hours after onset of infarction is considered to be

related to the original infarction itself. Pericarditis is probably not responsible for significant chest discomfort in the first 24 hours.

Pericarditis in acute MI occurs with extension of myocardial necrosis throughout the wall to the epicardium. The Multi-center Investigation of the Limitation of Infarct Size (MILIS) study<sup>211</sup> found that pericarditis (defined as the presence of a pericardial friction rub) occurred in 20% of 703 patients following acute MI. Postinfarction pericarditis occurs in approximately 25% of patients with acute transmural MI not treated with thrombolytic therapy when typical symptoms or a pericardial friction rub are accepted as indicative of pericarditis, whereas the average incidence is only 14% when the presence of a friction rub is required for the diagnosis.<sup>212</sup> Patients with pericarditis have larger infarcts (defined by CK-MB), lower ejection fraction (measured with radionuclide ventriculography), and a higher incidence of CHF.<sup>211,213</sup> Pericarditis may appear up to several weeks after acute MI. Anterior chest discomfort mimicking ischemia can occur with pericarditis. However, pericardial pain usually has distinguishing characteristics such as pleuritic or positional discomfort, radiation to the left shoulder, scapula or trapezius muscle and a pericardial rub, electrocardiographic J-point elevation with concave upward ST-segment elevation and PR depression. Pericardial effusion is evident echocardiographically in more than 40% of cases<sup>214</sup> but is rarely of hemodynamic consequence. A small effusion is not diagnostic of pericarditis as it can be demonstrated in the majority of patients with acute MI.<sup>87a</sup>

Focal pericarditis can be diagnosed electrocardiographically by either persistently positive T waves or reversal of initially inverted T waves during the first week after acute transmural MI. However, similar T-wave alterations have also been observed when postinfarction pericardial effusion exists in the absence of clinically recognized pericarditis.<sup>215</sup> Pericarditis is not associated with re-elevation of CK-MB, and there are data to suggest its incidence has decreased in the reperfusion era.<sup>216-218</sup> Interestingly, Dressler syndrome (post-MI syndrome), an autoimmune-type carditis, has essentially disappeared<sup>219</sup> in the reperfusion era.

Aspirin (160 to 325 mg daily) is the treatment of choice, but high doses (650 mg every 4 to 6 hours) may be required.<sup>220,221</sup> Indomethacin provides effective relief of symptoms; however, one study has presented data that suggest it may cause increased coronary vascular resistance<sup>222</sup> and experimentally causes thinning of developing scar.<sup>223</sup> Ibuprofen and corticosteroids, also efficacious for pain relief, exert a tendency for thinning of scar and myocardial rupture.<sup>224,225</sup> The risk-benefit ratio of continuing antithrombotic therapy such as heparin in the presence of acute pericarditis is always a clinical challenge. Usually such therapy can be continued safely but requires added vigilance for the detection of enlarging pericardial effusion or signs of hemodynamic instability. Any evidence of impending cardiac tamponade is an indication for prompt termination of antithrombotic therapy.

It is important to differentiate between pain due to pericar-

ditis and that due to ischemia. The latter is more likely when the chest pain is similar to the initial ischemic-type chest discomfort, occurring at rest or with limited activity during hospitalization. This may or may not be associated with re-elevation of the CK-MB, ST-segment depression or elevation, or pseudonormalization of inverted T waves (T-wave inversion on baseline ECG becoming upright during ischemia).<sup>214</sup> Early recurrent angina, especially after successful reperfusion, may occur in up to 58% of patients.<sup>226</sup>

Reinfarction has been reported to occur in approximately 10% of patients during the first 10 days but only in up to 3% to 4% of patients who have undergone thrombolytic therapy and received aspirin.<sup>97,227-230</sup> Reinfarction is associated with re-elevation of serum CK-MB after the initial peak of the index infarction. Diagnosis of reinfarction within 18 hours after initiation of thrombolytic therapy should be based on recurrence of severe ischemic-type chest discomfort lasting at least 30 minutes, usually, but not always, accompanied by recurrent ST-segment elevation of at least 0.1 mV in at least two contiguous ECG leads and re-elevation of CK-MB to more than the upper limit of normal or increased by at least 50% over the previous value.<sup>97</sup> Pathological findings of reinfarction show areas of healing myocardium along with the more recent necrosis usually in the same vascular risk region of myocardial tissue perfused by the original infarct-related artery. Death, severe CHF, and arrhythmias are early complications of reinfarction, and there is an increased incidence of cardiogenic shock or cardiac arrest.<sup>227,231</sup>

With recurrent suspected ischemic-type chest discomfort, coronary arteriography often clarifies the cause of chest discomfort with demonstration of a high-grade coronary obstruction. Prompt reperfusion using PTCA (if available and the lesion is suitable) or additional thrombolysis is appropriate, especially if a thrombus is present. If multiple high-grade lesions are present, more complete revascularization by CABG is appropriate.

Cardiac rupture may account for recurrent pain and occurs in 1% to 4% of all patients admitted with acute MI.<sup>230,232-234</sup> Left ventricular free wall rupture is typically heralded by chest pain and electrocardiographic ST-T wave changes with rapid progression to hemodynamic collapse and electromechanical dissociation. The frequency of cardiac rupture has two peaks: an early peak within 24 hours and a late one from 4 to 7 days after acute MI. Early rupture is related to the initial evolution of infarction before significant collagen deposition, and late rupture is related to expansion of the infarct-related ventricular wall.<sup>90,232</sup> Cardiac rupture is observed most frequently in patients with the first MI, those with anterior infarction, the elderly, and women. Other risk factors include hypertension during the acute phase of MI, lack of previous angina or MI, lack of collateral blood flow, Q waves on the ECG, use of corticosteroids or nonsteroidal anti-inflammatory drugs, and use of thrombolytic therapy more than 14 hours after onset.<sup>90,234</sup> However, thrombolytic therapy early after acute MI, ie, within 14 hours, decreases risk of cardiac rupture.<sup>91,233</sup> The most important determinants in preventing rupture are suc-

cessful early reperfusion and the presence of collateral circulation.<sup>232,233</sup> Pseudoaneurysm is a serious complication representing rupture of the free wall. Clot forms in the pericardial space, and an aneurysmal wall containing clot and pericardium prevents exsanguination. The echocardiogram characteristically shows a small neck opening into the body of the aneurysm.<sup>87a</sup> Surgical correction is always indicated.

Pericardiocentesis for relief of tamponade and emergency surgical repair may be lifesaving.<sup>235,236</sup> Transesophageal echocardiography is valuable in the diagnosis of free wall rupture and pseudoaneurysm, but for relief of tamponade in this setting, rapid fluid replacement is essential. Ideally the patient should be in the operating room and fully prepared for or already on cardiopulmonary bypass to prevent hemodynamic collapse.

## Heart Failure and Low-Output Syndromes

### Left Ventricular Dysfunction

Pump failure due to acute MI is manifested clinically by a weak pulse, poor peripheral perfusion with cool and cyanotic limbs, obtundation, and oliguria. Blood pressure (taken by cuff) is usually low, and there are variable degrees of pulmonary congestion. A third heart sound may be audible.

The treatment of LV dysfunction is determined by the specific hemodynamic derangements that are present, most importantly (1) pulmonary capillary wedge pressure, (2) cardiac output (measured with a balloon flotation catheter), and (3) systemic arterial pressure (preferably measured with an intra-arterial cannula). Often the patient has a cardiac index less than 2.5 L/min/m<sup>2</sup>, a modestly elevated left-sided filling pressure (greater than 18 mm Hg), and a systolic arterial pressure 100 mm Hg or greater. Although this subject has evidence of LV dysfunction, systemic arterial pressure is adequate to allow for (1) modest diuresis (best accomplished with intravenous furosemide) in combination with (2) afterload and preload reduction, using nitroglycerin. Nitroglycerin offers a greater degree of venodilation than sodium nitroprusside and relieves ischemia by dilating epicardial coronary arteries. In the early hours of acute infarction, when ischemia often contributes substantially to LV dysfunction, nitroglycerin is the more appropriate agent. Its intravenous infusion should be initiated at 5 µg/min and increased gradually until mean systolic arterial pressure falls by 10% to 15% but not below 90 mm Hg. The institution of ACE inhibitor therapy is also appropriate in this setting.

The patient with more severe LV dysfunction has a depressed cardiac output, an abnormally high left-sided filling pressure, and systolic arterial pressure less than 90 mm Hg; this patient has, or is rapidly approaching, cardiogenic shock. If the patient is markedly hypotensive, intravenous norepinephrine should be administered until systolic arterial pressure rises to at least 80 mm Hg, at which time a change to dopamine may be attempted, beginning at 5 to 15 µg/kg per minute. Once arterial pressure is brought to at least 90 mm Hg, intravenous dobutamine may be given simultaneously in an attempt to reduce the magnitude of the dopamine infusion. In addition,

consideration should be given to initiating intra-aortic balloon counterpulsation.

Recent nonrandomized and retrospective studies have suggested that mechanical reperfusion by PTCA or CABG of occluded coronary arteries may improve survival in patients with MI and cardiogenic shock. In large clinical trials such patients have an in-hospital survival rate ranging from 20% to 50% when treated with intravenous thrombolytic therapy.<sup>237-240</sup> In other case series mechanical reperfusion with PTCA has been reported to result in hospital survival rates as high as 70%, but selection bias may have influenced these findings. Multicenter, prospective, randomized studies are currently under way to verify these promising results.<sup>241</sup>

In the setting of cardiogenic shock complicating acute MI, emergency CABG has been used when other interventions have failed or not been indicated. A multicenter trial of surgically controlled reperfusion using total vented cardiopulmonary bypass and substrate-enhanced blood cardioplegia in patients with acute non-PTCA-related coronary occlusion noted 3.4% mortality overall with 9% mortality in patients with preoperative shock.<sup>242,243</sup> Data from the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) Registry suggest that, in some patients, emergency CABG (without specific recommendations regarding intraoperative myocardial protection strategies) is associated with lower mortality (19%) than emergency PTCA (60%) for patients with cardiogenic shock complicating acute MI.<sup>241</sup> In other nonrandomized studies surgical mortality ranged from 12%<sup>244</sup> to 42%<sup>245</sup> but is generally superior to other treatment modalities. The efficacy of emergency CABG in patients with cardiogenic shock may be better defined by an ongoing clinical trial.<sup>241</sup>

Based on these earlier studies, consideration for emergency CABG should be given for acute MI patients with multivessel disease or cardiogenic shock and who are *not* candidates for or who have undergone *unsuccessful* thrombolytic therapy and/or PTCA, and who are within 4 to 6 hours of onset of MI.

#### **Right Ventricular Infarction and Dysfunction**

*Right ventricular infarction* encompasses a spectrum of disease states ranging from asymptomatic mild right ventricular (RV) dysfunction through cardiogenic shock. Most patients demonstrate a return of normal RV function over a period of weeks to months, suggesting RV stunning has occurred rather than irreversible necrosis. In this sense RV ischemia can be demonstrated in up to half of all inferior MIs, although only 10% to 15% of patients show classical hemodynamic abnormalities.<sup>246,247</sup>

Right ventricular infarction accompanying inferior MIs is associated with a significantly higher mortality (25% to 30%) and thus identifies a high-risk subgroup of patients with inferior MIs (6%) who should be considered high-priority candidates for reperfusion.<sup>248</sup> One group of investigators recently reported a 31% in-hospital mortality rate in patients with inferior MIs complicated by RV infarction compared with 6% in patients who had an inferior MI without RV involve-

ment.<sup>246</sup> The treatment of patients with RV ischemia is different and occasionally diametrically opposed to management of LV dysfunction.

#### **Anatomic and Pathophysiological Considerations**

The right coronary artery usually supplies most of the RV myocardium; thus, occlusion of this artery proximal to the RV branches will lead to RV ischemia.<sup>248</sup> Hemodynamically significant RV infarctions occur almost exclusively in the setting of inferior acute MIs.<sup>249</sup> Because the right ventricle has a much smaller muscle mass than the left ventricle, due to the lower vascular resistance of the pulmonary circuit, myocardial oxygen demand is significantly less than that of the left ventricle.<sup>250</sup> Coronary perfusion of the right ventricle occurs in both systole and diastole.<sup>250</sup> The right ventricle also has a more favorable oxygen supply-demand ratio than the left ventricle, because of the more extensive collateral flow from left to right.<sup>251,252</sup> These factors likely explain the absence of hemodynamically significant RV ischemia in most patients with proximal right coronary artery occlusions, as well as improvement in RV function observed in the majority of patients following RV ischemia.<sup>253</sup>

The severity of the hemodynamic derangements associated with RV ischemia is related to (1) the extent of ischemia and subsequent RV dysfunction, (2) the restraining effect of the surrounding pericardium, and (3) interventricular dependence related to the shared interventricular septum. When the right ventricle becomes ischemic, it acutely dilates, resulting in an increased intrapericardial pressure caused by the restraining forces of the pericardium. As a consequence, there is a reduction in RV systolic pressure and output, decreased LV preload, a reduction in LV end-diastolic dimension and stroke volume, and a shifting of the interventricular septum toward the left ventricle.<sup>254</sup> Because of this RV systolic and diastolic dysfunction, the pressure gradient between the right and left atria becomes an important driving force for pulmonary perfusion. Factors that reduce preload (volume depletion, diuretics, nitrates) or diminish augmented right atrial contraction (concomitant atrial infarction, loss of AV synchrony), as well as factors that increase RV afterload (concomitant LV dysfunction), are likely to have profoundly adverse hemodynamic effects.<sup>255-257</sup> Goldstein and coworkers<sup>256</sup> have demonstrated the importance of a paradoxical interventricular septal motion that bulges in pistonlike fashion into the right ventricle, generating systolic force, which allows pulmonary perfusion. The loss of this compensatory mechanism with concomitant septal infarction may result in further deterioration in patients with RV ischemia.

#### **Clinical Diagnosis**

Evidence of RV ischemia should be sought in all patients with acute inferior MI. The clinical triad of hypotension, clear lung fields, and elevated jugular venous pressure in the setting of an inferior MI is characteristic of RV ischemia. Although specific, this triad has a sensitivity of less than 25%.<sup>258</sup> Distended neck veins alone or the presence of Kussmaul's sign

**Table 6.** Treatment Strategy for Right Ventricular Ischemia/Infarction

Maintain right ventricular preload
Volume loading (IV normal saline)
Avoid use of nitrates and diuretics
Maintain AV synchrony
AV sequential pacing for symptomatic high-degree heart block unresponsive to atropine
Prompt cardioversion for hemodynamically significant SVT
Inotropic support
Dobutamine (if cardiac output fails to increase after volume loading)
Reduce right ventricular afterload with left ventricular dysfunction
Intra-aortic balloon pump
Arterial vasodilators (sodium nitroprusside, hydralazine)
ACE inhibitors
Reperfusion
Thrombolytic agents
Primary PTCA
CABG (in selected patients with multivessel disease)

IV indicates intravenous; AV, atrioventricular; SVT, supraventricular tachycardia; ACE, angiotensin converting enzyme; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

(distention of the jugular vein on inspiration) are both sensitive and specific for RV ischemia in patients with an inferior MI.<sup>259</sup> These findings may be masked in the setting of volume depletion and may only become evident after adequate volume loading. A right atrial pressure of 10 mm Hg or greater and greater than 80% of pulmonary wedge pressure is a relatively sensitive and specific finding in patients with RV ischemia.<sup>260</sup>

Demonstration of 1 mm ST-segment elevation in the right precordial lead V<sub>4R</sub> is the single most predictive electrocardiographic finding in patients with RV ischemia.<sup>261</sup> The finding may be transient; half of patients show resolution of ST elevation within 10 hours of onset of symptoms.<sup>262</sup> It is important for physicians to ensure that hospital personnel (house officer, nurse, technician) recording the ECG in this setting know how to properly record lead V<sub>4R</sub>, especially in view of the variety of multilead recording systems available. All patients with inferior infarctions should be screened initially for this finding at the time of admission. Critical-care staff should be encouraged to choose routine monitoring leads based on infarct site. Echocardiography can be helpful in patients with suspicious but nondiagnostic findings.<sup>87a</sup> It can show RV dilation and asynergy, abnormal interventricular and interatrial septal motion, and even right to left shunting through a patent foramen ovale.<sup>263-265</sup> This latter finding is unique to RV ischemia and should be suspected when persistent hypoxia is not responsive to supplemental oxygen.<sup>265</sup>

#### Management of Right Ventricular Ischemia/Infarction

Treatment of RV infarction includes early maintenance of RV preload, reduction of RV afterload, inotropic support of the dysfunctional right ventricle, and early reperfusion<sup>73</sup> (Table 6). Because of their influence on preload, drugs routinely used in management of LV infarctions, such as nitrates and diuretics, may reduce cardiac output and produce severe

hypotension when the right ventricle is ischemic. Indeed, a common clinical presentation for RV infarction is profound hypotension following administration of sublingual nitroglycerin, with the degree of hypotension often out of proportion to the electrocardiographic severity of the infarct. Volume loading with normal saline alone often resolves accompanying hypotension and improves cardiac output.<sup>266</sup> In other cases, volume loading further elevates the right-sided filling pressure and RV dilatation, resulting in decreased LV output.<sup>267</sup> Although volume loading is a critical first step in the management of hypotension associated with RV ischemia, inotropic support (in particular, dobutamine hydrochloride) should be initiated if cardiac output fails to improve after 1 to 2 L of fluid has been given.

Another important factor for sustaining adequate RV preload is maintenance of AV synchrony. High-degree heart block is common, occurring in as many as half of these patients.<sup>268</sup> Atrioventricular sequential pacing leads to a significant increase in cardiac output and reversal of shock, even when ventricular pacing alone has not been of benefit.<sup>269</sup> Atrial fibrillation may occur in up to one third of patients with RV ischemia<sup>270</sup> and has profound hemodynamic effects. Prompt cardioversion from atrial fibrillation should be considered at the earliest sign of hemodynamic compromise. When LV dysfunction accompanies RV ischemia, the right ventricle is further compromised because of increased RV afterload and reduction in stroke volume.<sup>271</sup> In such circumstances, the use of afterload-reducing agents such as sodium nitroprusside or an intra-aortic counterpulsation device is often necessary to "unload" the left and subsequently the right ventricle.

Fibrinolytic therapy and primary PTCA with subsequent reperfusion have been shown to improve RV ejection fraction<sup>272</sup> and reduce the incidence of complete heart block.<sup>272-274</sup>

#### Prognosis

The mere presence of RV ischemia evident by noninvasive criteria is associated with significantly increased short-term morbidity and mortality and may also influence long-term outcome.<sup>246,275,276</sup> Clinical and hemodynamic recovery eventually occur even in patients with RV dysfunction<sup>259,277-279</sup> that persists for weeks or months. This return to normal may be due to improvement of concomitant LV dysfunction, resulting in a reduction in RV afterload, or to a gradual stretching of the pericardium with amelioration of its restraining effect.<sup>277</sup>

#### Hemodynamic Monitoring

##### Recommendations for Balloon Flotation Right-Heart Catheter Monitoring

###### Class I

1. Severe or progressive CHF or pulmonary edema.
2. Cardiogenic shock or progressive hypotension.
3. Suspected mechanical complications of acute infarction, ie, VSD, papillary muscle rupture, or pericardial tamponade.

**Class IIa**

1. Hypotension that does not respond promptly to fluid administration in a patient without pulmonary congestion.

**Class III**

1. Patients with acute infarction without evidence of cardiac or pulmonary complications.

The balloon flotation catheter is often very helpful in management of acute MI and concomitant hemodynamic instability, including low cardiac output, hypotension, persistent tachycardia, pulmonary edema, and apparent cardiogenic shock. In the patient with hypotension and tachycardia, the balloon flotation catheter allows quick and easy differentiation of (1) inadequate intravascular volume, with a resultant low left-sided filling pressure, and (2) adequate intravascular volume and a high left-sided filling pressure due to extensive LV dysfunction. Treatment of the former is prompt expansion of intravascular volume (with normal saline), whereas management of the latter often includes diuresis, inotropic support, afterload reduction, and/or other supportive measures. In those with extensive LV dysfunction, a balloon flotation catheter in the right side of the heart can be used to monitor therapeutic efforts to adjust the left-sided filling pressure so as to maximize cardiac output at the lowest possible filling pressure. These sophisticated manipulations of intracardiac pressures and cardiac output are usually made considerably easier with information provided by a flotation catheter.

Although the balloon flotation catheter is quite safe when used by experienced operators, its use has a recognized association with adverse events, including ventricular tachyarrhythmias (during its manipulation) and pulmonary hemorrhage or infarction. In addition, it causes some patient discomfort and requires that the patient be relatively immobile. Because the pressure waveform recorded from the catheter tip may be distorted, the clinician should routinely examine the actual waveform rather than rely on the digital display of pressure. Because of the risk of infection, balloon flotation catheters generally should not remain in the same site for more than 5 days.

#### **Recommendations for Intra-arterial Pressure Monitoring**

**Class I**

1. Patients with severe hypotension (systolic arterial pressure less than 80 mm Hg) and/or cardiogenic shock.
2. Patients receiving vasopressor agents.

**Class IIa**

1. Patients receiving intravenous sodium nitroprusside or other potent vasodilators.

**Class IIb**

1. Hemodynamically stable patients receiving intravenous nitroglycerin for myocardial ischemia.
2. Patients receiving intravenous inotropic agents.

**Class III**

1. Patients with acute infarction who are hemodynamically stable.

All CCUs should have the equipment and personnel to monitor intra-arterial pressure. Such monitoring is useful in all hypotensive patients, particularly those with cardiogenic shock. Long-term monitoring is best accomplished through the radial artery, although the brachial or femoral arteries may be used as alternatives. Perfusion of the limb or hand distal to the catheter site must be carefully and periodically examined for evidence of ischemia. Because of risk of arterial thrombosis and infection, intra-arterial catheters generally should not remain in the same arterial site for prolonged periods of time, certainly no longer than 72 hours. Intra-arterial and central catheters can be left in place for this amount of time only if carefully inserted and properly cared for with a sterile occlusive dressing. Before insertion, the site should be adequately prepared under sterile conditions. Antibacterial ointments are no longer recommended.<sup>280</sup>

#### **Recommendations for Intra-aortic Balloon Counterpulsation**

**Class I**

1. Cardiogenic shock not quickly reversed with pharmacological therapy as a stabilizing measure for angiography and prompt revascularization.
2. Acute mitral regurgitation or VSD complicating MI as a stabilizing therapy for angiography and repair/revascularization.
3. Recurrent intractable ventricular arrhythmias with hemodynamic instability.
4. Refractory post-MI angina as a bridge to angiography and revascularization.

**Class IIa**

1. Signs of hemodynamic instability, poor LV function, or persistent ischemia in patients with large areas of myocardium at risk.

**Class IIb**

1. In patients with successful PTCA after failed thrombolysis or those with three-vessel coronary disease to prevent reocclusion.
2. In patients known to have large areas of myocardium at risk with or without active ischemia.

Since its introduction in the late 1960s, intra-aortic balloon counterpulsation has been recognized as an effective treatment for patients with unstable ischemic syndromes and cardiogenic shock.<sup>281-286</sup> Reduction of LV afterload by rapid deflation of the balloon in end diastole appears to be the predominant mechanism of the balloon's effect.<sup>287,288</sup> By inflating in diastole, the balloon also raises diastolic coronary and systemic perfusion. Studies on the effects of this increased perfusion pressure on coronary blood flow and myocardial oxygen consumption have yielded conflicting results.<sup>289,290</sup> Recently Kern et al,<sup>291</sup> using Doppler flow velocity measurements, were able to show

a nearly twofold increase in proximal coronary flow velocity. This combination of decreased myocardial oxygen demand and maintained or improved coronary flow make intra-aortic balloon pumping a powerful tool for patients with cardiogenic shock or acute ischemic syndromes.

Counterpulsation was first used as a stand-alone modality to treat patients with post-MI cardiogenic shock.<sup>281</sup> Counterpulsation stabilized most patients, but in-hospital mortality remained a dismal 83%.<sup>281</sup> In virtually all shock-management strategies in which counterpulsation is used today, it acts as a stabilizing device or bridge to facilitate diagnostic angiography and revascularization or repair. In selected patient populations survival rates for cardiogenic shock treated in the first 16 to 24 hours with intra-aortic balloon pumping and surgical and angioplasty revascularization range between 60% and 75%.<sup>284,292</sup> Similarly, intra-aortic balloon pumping and early repair for acute VSD and mitral regurgitation show survival rates of 60% or sometimes higher.<sup>285</sup> Patients with severe recurrent ischemia after MI can be stabilized with an intra-aortic balloon pump so that they can undergo angiography and emergency revascularization with PTCA or CABG.<sup>240</sup>

Several early studies, before reperfusion therapy, showed that routine prophylactic use of intra-aortic balloon pumping in acute MI<sup>282,293</sup> did not affect infarct size. A retrospective review of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials suggested that placement of an intra-aortic balloon pump after reperfusion with either thrombolytic therapy or PTCA reduced the incidence of reocclusion.<sup>294</sup> In a subsequent randomized trial, patients with rescue PTCA at 90 minutes or those with three-vessel CAD<sup>295</sup> showed a reduction of reocclusion events from 21% to 8% after intra-aortic balloon pumping. In a second randomized trial of the use of prophylactic placement of these devices in high-risk patients (age greater than 70, ejection fraction less than 45%, three-vessel disease, suboptimal PTCA, saphenous graft occlusion, ventricular arrhythmias) undergoing primary PTCA, 437 patients were studied to determine the effect of balloon pumping on resulting LV function and a composite clinical end point (death, reocclusion, reinfarction, CHF, and stroke). There was no significant difference in clinical outcome, including rate of reocclusion (6.2% versus 8.0%), nor did it influence global or regional LV function.<sup>296</sup> However, there was a reduction in the incidence of recurrent ischemia, including the need for repeat angiography and PTCA of the infarct-related artery. In summary, for patients without LV dysfunction, the prophylactic and routine use of intra-aortic balloon pumping following either reperfusion strategy cannot be recommended.

### Rhythm Disturbances

#### Atrial Fibrillation

#### Recommendations

##### Class I

1. Electrical cardioversion for patients with severe hemodynamic compromise or intractable ischemia.

2. Rapid digitalization to slow a rapid ventricular response and improve LV function.

3. Intravenous  $\beta$ -adrenoceptor blockers to slow a rapid ventricular response in patients without clinical LV dysfunction, bronchospastic disease, or AV block.

4. Heparin should be given.

##### Class IIa

1. Either diltiazem or verapamil intravenously to slow a rapid ventricular response if  $\beta$ -adrenoceptor blocking agents are contraindicated or ineffective.

Atrial fibrillation (AF) associated with acute MI most often occurs within the first 24 hours and is usually transient but may recur. The incidence of AF in acute MI ranges from 10% to 16%,<sup>297,298</sup> whereas atrial flutter or supraventricular tachycardia is much less frequent. The consequences and acute treatment of all three conditions may be considered together, recognizing that in atrial flutter and supraventricular tachycardia, atrial pacing may be effective in terminating the tachycardia.<sup>299-305</sup> The incidence of AF increases with age, occurring in 4.2% of patients aged 59 years or less and in 16% of patients aged 70 or older. Atrial fibrillation occurs more often in patients with larger infarcts, those anterior in location, and in patients whose hospital course is complicated by CHF, complex ventricular arrhythmias, advanced AV block, atrial infarction, or pericarditis. Atrial fibrillation may also occur in patients with inferior MI secondary to proximal right coronary artery occlusion due to involvement of the sinoatrial nodal artery, which provides the major blood supply to the atria.

The incidence of AF after acute MI is decreased in patients receiving thrombolytic therapy,<sup>300,306</sup> and in the GUSTO trial patients treated with accelerated alteplase and intravenous heparin had a significantly lower incidence of AF and atrial flutter compared with other fibrinolytic therapies.<sup>228</sup> The occurrence of AF is also associated with excess catecholamine release, hypokalemia, hypomagnesemia, hypoxia, underlying chronic lung disease, and ischemia of the sinus node or left atrial circumflex arteries.<sup>270,297,300,307-310</sup>

Systemic embolization is more frequent in patients with paroxysmal AF (1.7%) compared with those without (0.6%), with one half of embolic events occurring on the first day of hospitalization and more than 90% occurring by the fourth day.<sup>298</sup> Because AF can be associated with pericarditis, the development of PR-segment displacement on serial ECGs may predict risk of developing AF during hospitalization.<sup>306</sup>

When hemodynamic compromise occurs due to rapid ventricular rate or loss of atrial contraction, immediate cardioversion is indicated, beginning with 100 J, then 200 to 300 J, then 360 J if lower energies fail. In the conscious patient, support with brief anesthesia is essential.

In the absence of CHF or severe pulmonary disease, one of the most effective means of slowing the ventricular rate in AF is the use of intravenous  $\beta$ -adrenoceptor blocking agents such as atenolol (2.5 to 5.0 mg over 2 minutes to a total of 10 mg in 10 to 15 minutes) or metoprolol (2.5 to 5.0 mg every 2 to 5

minutes to a total of 15 mg over 10 to 15 minutes). Heart rate, blood pressure, and the ECG should be monitored, and treatment should be halted when therapeutic efficacy is achieved or if systolic blood pressure falls below 100 mm Hg or heart rate below 50 bpm during treatment.

Rapid administration of digitalis to achieve rate slowing may be accomplished by giving intravenous digoxin (8 to 15  $\mu\text{g}/\text{kg}$  [0.6 to 1.0 mg in a person weighing 70 kg]) with half the dose administered initially and the additional increment in 4 hours.<sup>221</sup> This method provides a slower response than intravenous  $\beta$ -adrenoceptor blockade; however, some effect on rate slowing may be detectable in one half to 2 hours.

Rate slowing may also be achieved by intravenous verapamil (5 to 10 mg [0.075 to 0.15 mg/kg]) given over 2 minutes with a repeat dose 30 minutes later or similarly by intravenous bolus administration of diltiazem (20 mg [0.25 mg/kg]) over 2 minutes followed by an infusion of 10 mg/h. If rate response is inadequate, a second dose of diltiazem (25 mg [0.35 mg/kg]) may be given over 2 minutes after an interval of 15 minutes. A subsequent infusion is given at a rate of 10 to 15 mg/h. Because of their negative inotropic effect and newer concerns regarding the use of calcium channel blockers in acute MI, these agents are not recommended as first-line drugs despite their effectiveness in slowing heart rate, especially if given to patients also receiving  $\beta$ -blocking agents.<sup>311</sup> Although AF after acute MI is usually transient, heparin therapy should be given to patients not already receiving it.

Guidelines for use of Class I and Class III antiarrhythmic agents and electric shock for converting persistent AF have not been formulated. It is not clear whether antiarrhythmic agents should be used for prevention of AF if it recurs during hospitalization, although its recurrence portends a worse prognosis.<sup>305</sup> For this reason it has become common practice to use antiarrhythmic agents such as quinidine, procainamide, or, preferably, amiodarone or sotalol.<sup>312</sup> Transient AF does not obligate the patient to receive long-term anticoagulation or antiarrhythmic agents, but if such treatment is elected, it is appropriate to limit their use to 6 weeks if sinus rhythm has been restored.

### Ventricular Tachycardia/Ventricular Fibrillation

#### Recommendations

##### *Class I*

1. Ventricular fibrillation should be treated with an unsynchronized electric shock with an initial energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J.

2. Sustained (more than 30 seconds or causing hemodynamic collapse) polymorphic VT should be treated with an unsynchronized electric shock using an initial energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J.

3. Episodes of sustained monomorphic VT associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with a synchronized

electric shock of 100 J initial energy. Increasing energies may be used if not initially successful.

4. Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with one of the following regimens:

- a. Lidocaine: bolus 1.0 to 1.5 mg/kg. Supplemental boluses of 0.5 to 0.75 mg/kg every 5 to 10 minutes to a maximum of 3 mg/kg total loading dose may be given as needed. Loading is followed by infusion of 2 to 4 mg/min (30 to 50  $\mu\text{g}/\text{kg}$  per minute).

- b. Procainamide: 20 to 30 mg/min loading infusion, up to 12 to 17 mg/kg. This may be followed by an infusion of 1 to 4 mg/min.

- c. Amiodarone: 150 mg infused over 10 minutes followed by a constant infusion of 1.0 mg/min for 6 hours and then a maintenance infusion of 0.5 mg/min.

- d. Synchronized electrical cardioversion starting at 50 J (brief anesthesia is necessary).

*Comment: Knowledge of the pharmacokinetics of these agents is important because dosing varies considerably, depending on age, weight, and hepatic and renal function.*

#### *Class IIa*

1. Infusions of antiarrhythmic drugs may be used after an episode of VT/VF but should be discontinued after 6 to 24 hours and the need for further arrhythmia management assessed.

2. Electrolyte and acid-base disturbances should be corrected to prevent recurrent episodes of VF when an initial episode of VF has been treated.

#### *Class IIb*

1. Drug-refractory polymorphic VT should be managed by aggressive attempts to reduce myocardial ischemia, including therapies such as  $\beta$ -adrenoceptor blockade, intra-aortic balloon pumping, and emergency PTCA/CABG surgery. Amiodarone, 150 mg infused over 10 minutes followed by a constant infusion of 1.0 mg/min for up to 6 hours and then a maintenance infusion at 0.5 mg/min, may also be helpful.

#### *Class III*

1. Treatment of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, and nonsustained VT.

2. Prophylactic administration of antiarrhythmic therapy when using thrombolytic agents.

### Ventricular Fibrillation—Background

Disturbances of cardiac rhythm are common during acute MI. Early-phase arrhythmias are probably largely a result of micro reentry. Although other electrophysiological mechanisms such as enhanced automaticity and triggered activity have been proposed in experimental models of MI, convincing evidence of their role in human MI is not yet established.<sup>313</sup> Important contributory factors include heightened adrenergic nervous system tone, hypokalemia, hypomagnesemia, intracel-

lular hypercalcemia, acidosis, free fatty acid production from lipolysis, and free radical production from reperfusion of ischemic myocardium.<sup>313-315</sup> The relative importance of each of these factors in the pathogenesis of arrhythmias during acute MI has not been established, nor has it been clearly shown that aggressive measures specifically targeted at one or more of these mechanisms can be relied on clinically to reduce arrhythmia frequency in acute MI.

Primary VF should be distinguished from secondary VF, the latter occurring in the presence of severe CHF or cardiogenic shock.<sup>316</sup> Late VF develops more than 48 hours after onset of infarction. The incidence of primary VF is highest (around 3% to 5%) in the first 4 hours after MI and declines markedly thereafter.<sup>317</sup> Epidemiological data suggest that the incidence of primary VF in acute MI may be decreasing in the current era, possibly due to aggressive attempts at infarct-size reduction, correction of electrolyte deficits, and a greater use of  $\beta$ -adrenoceptor blocking agents.<sup>318</sup> Contrary to prior belief, primary VF appears to be associated with a significantly higher in-hospital mortality, but those persons who survive to hospital discharge have the same long-term prognosis as patients who do not experience primary VF.<sup>319</sup>

### *Management Strategies for Ventricular Fibrillation*

#### **PROPHYLAXIS**

Primary VF remains an important contributor to risk of mortality during the first 24 hours after MI. Therefore, a reliable method for its prediction and prevention remains desirable but has not been established despite extensive clinical investigation. Classification of ventricular arrhythmias in ascending order of risk of primary VF ("warning arrhythmias") was proposed, but this approach lacks appropriate specificity and sensitivity.<sup>320-322</sup>

Accelerated idioventricular rhythm occurs frequently during the first 12 hours of infarction. Data from the prereperfusion era do not support development of accelerated idioventricular rhythm as a risk factor for development of VF.<sup>321,323</sup> In patients receiving thrombolysis or undergoing primary PTCA, accelerated idioventricular rhythm may be a reperfusion arrhythmia and does not indicate an increased risk of VF.<sup>324</sup> Thus, it is best managed by observation and should not trigger initiation of antiarrhythmic prophylaxis against VF.

Meta-analysis of randomized trials of prophylaxis with lidocaine has shown a reduction in the incidence of primary VF by about 33%, but this was offset by a trend toward increased mortality, probably from fatal episodes of bradycardia and asystole.<sup>325</sup> The prior practice of routine ("prophylactic") administration of lidocaine to all patients with known or suspected MI has been largely abandoned in most contemporary CCU protocols because of an unfavorable risk-benefit ratio and a decreased incidence of the target arrhythmia. Thus, its routine use is not recommended, with the possible exception being situations in which a defibrillator is unavailable, provided there is a skilled professional always available who can initiate CPR if asystole occurs. Prophylactic regimens with

other antiarrhythmic drugs have not been evaluated as extensively as lidocaine, and no other agents, even including the close structural analogues mexiletine and tocainide, have been shown to decrease the incidence of primary VF when given on a prophylactic basis.

Routine administration of intravenous  $\beta$ -adrenoceptor blockers to patients without hemodynamic or electrical (AV block) contraindications is associated with a reduction in incidence of early VF. Intravenous followed by oral  $\beta$ -adrenoceptor blockers should be given in the absence of contraindications. Suitable regimens include intravenous metoprolol (5 mg every 2 minutes for 3 doses, if tolerated, followed by 50 mg orally twice a day for at least 24 hours and then increased to 100 mg twice a day). An alternative regimen is atenolol (5 to 10 mg intravenously followed by 100 mg orally on a daily basis).

Clinical experience as well as observational data from CCU populations has identified hypokalemia as an arrhythmogenic risk factor for VF.<sup>314,315</sup> Low serum levels of magnesium have not been clearly shown to be associated with an increased risk of VF,<sup>315</sup> although tissue depletion of magnesium remains a potential risk factor. Although randomized clinical trial data do not exist to confirm the benefits of repletion of potassium and magnesium deficits in preventing VF, it is sound clinical practice to maintain serum potassium levels at greater than 4.0 mEq/L and magnesium levels at greater than 2.0 mEq/L in patients with acute MI.

#### **TREATMENT**

Ventricular fibrillation should be treated with an unsynchronized electric shock using an initial energy of 200 J. If this is unsuccessful, a second shock using 200 to 300 J and, if necessary, a third shock using 360 J is indicated.<sup>326</sup> Ventricular fibrillation that is not easily converted by defibrillation may be treated with additional adjunctive measures. No rigorous scientific support exists to favor one pharmacological treatment program over another or even to confirm that they improve the likelihood of resuscitation over repeated shocks given alone. The ACLS protocol recommends adjunctive therapy in the following hierarchy, as needed, for resistant VF<sup>326</sup>: (1) epinephrine (1 mg IV push); (2) lidocaine (1.5 mg/kg); (3) bretylium (5 to 10 mg/kg). Intravenous amiodarone (150 mg bolus), now available, also may be used.

There are no firm data to help define an optimal management strategy for prevention of recurrent VF in patients who have sustained an initial episode of VF in the setting of MI. It seems prudent to correct any electrolyte and acid-base disturbances and administer  $\beta$ -adrenoceptor-blocking agents to inhibit increased sympathetic nervous system tone and prevent ischemia.<sup>313</sup> If infusion of an antiarrhythmic drug is initiated (eg, lidocaine 2 mg/min), it should probably be maintained for only 6 to 24 hours and then discontinued so that the patient's ongoing need for antiarrhythmic treatment can be reassessed.

### Ventricular Tachycardia—Background

Several definitions have been used for VT in the setting of acute MI. Nonsustained VT lasts less than 30 seconds, whereas sustained VT lasts more than 30 seconds and/or causes earlier hemodynamic compromise requiring immediate intervention. Based on electrocardiographic appearance, VT has also been categorized as monomorphic or polymorphic. While short bursts (fewer than 5 beats) of nonsustained VT of either monomorphic or polymorphic configuration may be seen frequently, contemporary epidemiological data do not suggest that they are associated with a sufficiently increased risk of sustained VT or VF to warrant a recommendation of prophylactic therapy.

The vast majority of post-MI VT and VF occur within the first 48 hours of MI.<sup>317</sup> Sustained VT or VF occurring outside of this time frame deserves careful evaluation, including consideration of electrophysiology studies. In addition, monomorphic VT at rates less than 170 bpm are unusual as a post-MI arrhythmia and suggests a more chronic (mature) arrhythmogenic substrate.<sup>327-330</sup>

### Management Strategies for Ventricular Tachycardia

1. Only for episodes of sustained hemodynamically compromising VT is treatment always indicated.<sup>313</sup> In the absence of clinical evidence of effective perfusion, urgent electrical conversion of VT is indicated. Rapid, polymorphic-appearing VT should be considered similar to VF and managed with an unsynchronized discharge of 200 J, while monomorphic VT with rates greater than 150 bpm can usually be treated with a 100-J synchronized discharge.<sup>326</sup> If the patient is hemodynamically stable, brief trials of medications (lidocaine or procainamide) may be given first. Immediate cardioversion is generally not needed for rates under 150 bpm.

2. Episodes of sustained VT that are somewhat better tolerated hemodynamically may initially be treated with one of the following drug regimens:

a. Lidocaine: bolus 1.0 to 1.5 mg/kg. Supplemental boluses of 0.5 to 0.75 mg/kg every 5 to 10 minutes to a maximum of 3 mg/kg total loading dose may be given as needed. Loading is followed by infusion of 2 to 4 mg/min (30 to 50 µg/kg per minute). In older patients and those with CHF or hepatic dysfunction, infusion rates should be reduced to avoid lidocaine toxicity.

b. Procainamide: 20 to 30 mg/min loading infusion, up to 12 to 17 mg/kg. This may be followed by an infusion of 1 to 4 mg/min. Infusion rates should be lower in the presence of renal dysfunction.

c. Amiodarone: 150 mg infused over 10 minutes followed by a constant infusion of 1.0 mg/min for 6 hours and then a maintenance infusion at 0.5 mg/min.

3. Rare episodes of drug-refractory sustained polymorphic VT ("electrical storm") have been reported in cases of acute MI. Anecdotal evidence suggests that these may be related to uncontrolled ischemia and increased sympathetic tone and are best treated by intravenous β-adrenoceptor

blockade,<sup>331</sup> intravenous amiodarone,<sup>332</sup> intra-aortic balloon pumping, or emergency revascularization.

### Bradyarrhythmias and Heart Block

#### Background, Epidemiology, and Importance

Sinus bradycardia occurs frequently (in 30% to 40% of patients) with acute MI, especially within the first hour of inferior MI and with reperfusion of the right coronary artery (Bezold-Jarisch reflex), a result of increased parasympathetic activity (vagal tone).<sup>97</sup> Heart block may develop in approximately 6% to 14% of patients with acute MI and predicts an increased risk of in-hospital mortality but is a poor predictor of long-term mortality in those surviving to discharge.<sup>333-335</sup> Intraventricular conduction delay has been reported in about 10% to 20% of patients with acute MI in past reviews.<sup>336</sup> Of acute MI patients entered in recent thrombolysis trials, BBB was present on admission in only 4% but predicted a substantially increased in-hospital mortality.<sup>27</sup>

The increased mortality associated with heart block and intraventricular conduction delay is related more to extensive myocardial damage than to heart block as such. Indeed, pacing has not been clearly shown to reduce mortality associated with AV block or intraventricular conduction delay.<sup>334,337</sup> The difficulty in showing benefit may reflect the overriding impact on mortality of extensive infarction that may obscure benefit in a fraction of these patients.<sup>337,338</sup> Thus, pacing to protect against sudden hypotension, acute ischemia, and precipitation of ventricular arrhythmias associated with sudden heart block is still recommended in selected high-risk patients.

#### Prognosis

Prognosis in AV block is related to the site of infarction (anterior versus inferior), the site of block (intranodal [proximal]—above the His bundle—versus infranodal [distal]—below the His bundle), the nature of the escape rhythm, and the hemodynamic consequences.<sup>221,337-339</sup>

The risk of developing heart block with acute MI is increased when one or more of the following are present: first-degree AV block, Mobitz type I AV block, Mobitz type II AV block, left anterior hemiblock, left posterior hemiblock, right bundle branch block (RBBB), and LBBB.

#### Treatment

#### Recommendations for Atropine (also see "Initial Recognition and Management in the Emergency Department" for early use)

##### Class I

1. Symptomatic sinus bradycardia (generally, heart rate less than 50 bpm associated with hypotension, ischemia, or escape ventricular arrhythmia).
2. Ventricular asystole.
3. Symptomatic AV block occurring at the AV nodal level (second-degree type I or third degree with a narrow-complex escape rhythm).

**Class IIa**

None.

**Class III**

1. Atrioventricular block occurring at an infranodal level (usually associated with anterior MI with a wide-complex escape rhythm).

2. Asymptomatic sinus bradycardia.

Atropine reverses decreases in heart rate, systemic vascular resistance, and blood pressure mediated by parasympathetic (cholinergic) activity. Atropine is useful for treating symptomatic sinus bradycardia, and may be beneficial in the presence of AV block at the AV node level or for ventricular asystole.<sup>326</sup> Atropine is most effective for sinus bradycardia occurring within 6 hours of onset of symptoms of acute MI.<sup>336</sup> Sinus bradycardia at this time may be related to ischemia, reperfusion (Bezold-Jarisch reflex), ischemic-type chest discomfort, or morphine or nitroglycerin therapy. Atropine is also effective for profound sinus bradycardia with hypotension associated with thrombolytic therapy (especially of the right coronary artery).<sup>340</sup> Atropine should be used with caution in the setting of acute MI because of the protective effect of parasympathetic tone against VF and myocardial infarct extension.<sup>326,341</sup> Doses in increments of 0.5 mg, titrated to achieve minimally effective heart rate (for example, about 60 bpm), up to a maximum of 2.0 mg, may be given.<sup>342</sup> (Doses less than 0.5 mg occasionally may elicit a parasympathomimetic response with a paradoxical slowing of heart rate.)

**Temporary Pacing**

Pacing recommendations in these revised guidelines place more emphasis on transcutaneous pacing.<sup>1</sup> The newly available transcutaneous pacemaker systems are suitable for providing standby pacing in acute MI, especially for those not requiring immediate pacing and at only moderate risk of progression to AV block, and do not entail the difficulty in application and risk of complications of intravenous systems.<sup>343,344</sup> Transcutaneous technology is also well suited to patients receiving thrombolytic therapy, reducing the need for vascular interventions.

**Recommendations for Placement of Transcutaneous Patches\* and Active (Demand) Transcutaneous Pacing†<sup>326</sup>**

**Class I**

1. Sinus bradycardia (rate less than 50 bpm) with symptoms of hypotension (systolic blood pressure less than 80 mm Hg) unresponsive to drug therapy.†

\*Transcutaneous patches applied; system may be attached and activated within a brief time if needed. Transcutaneous pacing may be very helpful as an urgent expedient. Because it is associated with significant pain, high-risk patients likely to require pacing should receive a temporary pacemaker.

†Apply patches and attach system; system is in either active or standby mode to allow immediate use on demand as required. In facilities in which transvenous pacing or expertise are not available to place an IV system, consideration should be given to transporting the patient to one equipped and competent in placing transvenous systems.

2. Mobitz type II second-degree AV block.‡
3. Third-degree heart block.‡
4. Bilateral BBB (alternating BBB, or RBBB and alternating left anterior fascicular block [LAFB], left posterior fascicular block [LPFB]) (irrespective of time of onset).\*
5. Newly acquired or age indeterminate LBBB, LBBB and LAFBa, RBBB and LPFB.\*
6. RBBB or LBBB and first-degree AV block.\*

**Class IIa**

1. Stable bradycardia (systolic blood pressure greater than 90 mm Hg, no hemodynamic compromise, or compromise responsive to initial drug therapy).\*
2. Newly acquired or age-indeterminate RBBB.\*

**Class IIb**

1. Newly acquired or age-indeterminate first-degree AV block.\*

**Class III**

1. Uncomplicated acute MI without evidence of conduction system disease.

Transcutaneous systems are available that use a single pair of adequately sized, multifunctional electrodes that allow electrogram monitoring, transcutaneous pacing, and defibrillation as needed. These systems may be used in a standby mode in potentially unstable patients. Because transcutaneous pacing may be uncomfortable, especially when prolonged, it is intended to be prophylactic and temporary. A transvenous pacing electrode should be placed in patients who require ongoing pacing and in those with a very high probability of requiring pacing (risk of AV block of 30% or more). Thus, transcutaneous pacing systems have allowed both the broadening of the application of standby pacing and the narrowing of the application of transvenous pacing. Technical aspects of transcutaneous pacing are reviewed elsewhere.<sup>345</sup> The revised recommendations reflect this change.

**Recommendations for Temporary Transvenous Pacing‡**

**Class I**

1. Asystole.
2. Symptomatic bradycardia (includes sinus bradycardia with hypotension and type I second-degree AV block with hypotension not responsive to atropine).
3. Bilateral BBB (alternating BBB or RBBB with alternating LAFB/LPFB) (any age).
4. New or indeterminate age bifascicular block (RBBB with LAFB or LPFB, or LBBB) with first-degree AV block.
5. Mobitz type II second-degree AV block.

‡It should be noted that in choosing an intravenous pacemaker system, patients with substantially depressed ventricular performance, including RV infarction, may respond better to atrial/AV sequential pacing than ventricular pacing.<sup>346,347</sup>

**Class IIa (note also "Recommendations for Transcutaneous Standby Pacing" above)**

1. RBBB and LAFB or LPFB (new or indeterminate).
2. RBBB with first-degree AV block.
3. LBBB, new or indeterminate.
4. Incessant VT, for atrial or ventricular overdrive pacing.
5. Recurrent sinus pauses (greater than 3 seconds) not responsive to atropine.

**Class IIb**

1. Bifascicular block of indeterminate age.
2. New or age-indeterminate isolated RBBB.

**Class III**

1. First-degree heart block.
2. Type I second-degree AV block with normal hemodynamics.
3. Accelerated idioventricular rhythm.
4. Bundle branch block or fascicular block known to exist before acute MI.

Transvenous access to the right heart (ie, RV apex) with a catheter for temporary pacing can be achieved percutaneously through the internal (or external) jugular, subclavian, or femoral veins and through the brachial veins, percutaneously or by cutdown.<sup>348</sup> Details of pacemaker placement are provided elsewhere.<sup>345</sup> Review of the clinical course of 1022 consecutive patients who received a temporary transvenous pacemaker in the CCU during a 5-year period at Mayo Clinic<sup>348</sup> suggests that the preferred routes of insertion, especially if fluoroscopy is not immediately available, are the right internal jugular vein (generally first choice) or left subclavian vein (second choice), provided that the operator is well-trained in venous access at these sites. In overall experience, loss of ventricular capture was observed in 18% of patients and complications in 14% (without associated mortality). The highest rates of loss of capture and pacemaker-related complications occurred with brachial venous pacing.

Choosing between ventricular (single-chamber) and sequential, AV (dual-chamber) pacing forms part of the decision-making process when proceeding with transvenous pacing. Because of its greater ease and reliability, ventricular pacing with a single lead is usually chosen. However, selected patients may require AV synchrony to maintain adequate hemodynamic compensation, especially those who are pacemaker dependent. In these cases, an atrial J-lead is also placed and guided to the right atrial appendage fluoroscopically. Alternatively, coronary sinus pacing may be used. Patients with RV infarction and other acute MIs with substantially impaired systolic and/or diastolic function are frequently best treated with AV sequential pacing.

Once placed, temporary transvenous pacing may be performed in bipolar or unipolar configurations using a variety of commercially available leads.<sup>345</sup> Temporary pacing requires meticulous oversight to ensure safety and efficacy. Temporary pacemaker care is best provided in an intensive care unit setting (generally the CCU). Care includes ensuring sterility of

the venous access site and securely attaching the transvenous lead to the skin; attending to appropriate function and settings of the rate, mode, and threshold functions of the external generator box; continuous monitoring to ensure appropriate pacing and sensing functions and absence of dislodgment; and frequent (eg, at least once per shift) testing of pacing thresholds (pacing energy is usually set at more than three times the threshold).

**Permanent Pacing After Acute Myocardial Infarction**

Use of permanent pacemakers after acute MI is addressed in the ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices.<sup>349</sup> The requirement for temporary pacing in acute MI does not by itself constitute an indication for permanent pacing. The unfavorable long-term prognosis of patients with acute MI that has caused conduction disturbances is related primarily to the extent of associated myocardial injury. Consequently these patients are at greater risk for death from heart failure and ventricular tachyarrhythmia than from progressive heart block. Indications for permanent pacing after acute MI in patients experiencing conduction disturbances are related primarily to the degree and type of AV block and do not necessarily depend on the presence of symptoms.

**Recommendations****Class I**

1. Persistent second-degree AV block in the His-Purkinje system with bilateral BBB or complete heart block after acute MI.
2. Transient advanced (second- or third-degree) AV block and associated BBB.\*
3. Symptomatic AV block at any level.

**Class IIb**

1. Persistent advanced (second- or third-degree) block at the AV node level.

**Class III**

1. Transient AV conduction disturbances in the absence of intraventricular conduction defects.
2. Transient AV block in the presence of isolated LAFB.
3. Acquired LAFB in the absence of AV block.
4. Persistent first-degree AV block in the presence of BBB that is old or age indeterminate.

**Other Surgical Interventions****Recommendations for Emergency or Urgent Cardiac Repair of Mechanical Defects****Class I**

1. Papillary muscle rupture with severe acute mitral insufficiency.

\*An electrophysiology study should be considered to assess the site and extent of heart block in uncertain cases.

**2. Postinfarction VSD or free wall rupture and pulmonary edema or cardiogenic shock (emergency or urgent).**

**3. Postinfarction ventricular aneurysm associated with intractable ventricular tachyarrhythmias and/or pump failure (urgent).**

**Class III**

**1. Acute infarctectomy in hemodynamically stable patients.**

**Clinical Situations Leading to Coronary Artery Bypass Graft Surgery**

**Evolving Myocardial Infarction**

The role of emergency CABG for evolving MI has been discussed in "Initial Recognition and Management in the Emergency Department." The prevailing opinion at this time is that CABG should be limited to patients who have suitable surgical anatomy and who are not candidates for or who have failed thrombolytic therapy/PTCA and who are within 4 to 6 hours of the onset of MI.

In the setting of cardiogenic shock complicating acute MI, emergency CABG has been used when other interventions have failed or have not been indicated. This topic has been discussed in "Initial Recognition and Management in the Emergency Department."

**Failed Percutaneous Transluminal Coronary Angioplasty**

Emergency CABG is indicated for most patients with acute MI who have persistent angina pectoris or hemodynamic instability following failed PTCA. Coronary artery bypass graft surgery, optimally performed within 2 to 3 hours, can limit myocardial necrosis. However, mortality (3.7% to 12.0%) and morbidity rates exceed those for elective CABG, in particular postoperative hemorrhage, the need for blood products, and perioperative MI (21% to 43% in unstable patients). Operative mortality is increased in patients with unstable hemodynamic status, myocardial ischemia, multivessel disease, and prior CABG.<sup>350,351</sup>

**Postthrombolytic Therapy**

For the 3339 patients enrolled in the TIMI-II trial, CABG was used emergently (1.6%) or electively (10% during initial hospitalization), primarily for left main coronary stenosis or coronary anatomy not amenable to PTCA and continuing, recurrent, or exercise-induced ischemia.<sup>352</sup> For the 41 021 patients enrolled in the GUSTO trial, CABG was used in 8.6% at a mean of 8.5 days following thrombolytic therapy.<sup>353</sup> Unstable patients undergoing CABG shortly after thrombolytic therapy, primarily for continuing myocardial ischemia, have a higher operative mortality (13% to 17%) and increased use of blood products<sup>352,354,355</sup> than hemodynamically stable patients operated on within 8 hours of thrombolytic therapy, who have a relatively low (2.8%) mortality.<sup>356</sup> The only independent predictor of perioperative mortality in TIMI-II was performance of CABG within 24 hours of entry or PTCA. The low 1-year mortality rate (2.2%) noted for operative survivors in this group may support the use of emergency operation for

selected patients, however.<sup>352</sup> The intraoperative use of aprotinin may reduce hemorrhage related to use of thrombolytic agents.<sup>357</sup>

**Recurrent Ischemia**

Urgent CABG should be considered when recurrent ischemia occurs in patients who have sustained an acute MI and whose coronary artery anatomy is not suitable for PTCA. Operative mortality in such patients is correlated closely with ejection fraction, and for patients with normal ejection fraction is nearly the same as that of elective CABG.<sup>358-360</sup> The survival benefit for patients with reduced LV function supports the use of CABG in this situation.

**Elective Coronary Artery Bypass Graft Surgery After Acute Myocardial Infarction**

Elective CABG would be expected to improve long-term survival in patients with MI who have left main coronary artery stenosis (greater than 50%), three-vessel disease, two-vessel disease with proximal left anterior descending coronary artery stenosis, or two-vessel disease not amenable to PTCA and reduced ejection fraction.<sup>128</sup> The optimal timing of surgery has not been established in a randomized controlled trial, although recent retrospective reports have suggested that elective CABG may be carried out 3 to 7 days after MI with operative mortality approaching that for other elective CABG. Risk of operation is increased for patients with emergency or urgent surgery, older age, and poor ventricular function.<sup>360-365</sup>

**Ventricular Tachyarrhythmias**

Ventricular tachyarrhythmia is not an indication for emergency CABG except in rare circumstances when refractory ventricular tachyarrhythmia is thought to be due to ischemia. Intra-aortic balloon pump support has been successful in temporarily reducing the incidence of refractory ventricular tachyarrhythmia in some cases.<sup>366</sup>

**Patients With Prior Coronary Artery Bypass Graft Surgery**

Progression of atherosclerosis, particularly in saphenous vein bypass grafts, can result in recurrent myocardial ischemia and the need for reintervention.<sup>367</sup> These patients typically have an increased prevalence of unfavorable risk factors, such as previous MI, lower ejection fraction, CHF, and other comorbid conditions as well as risk of atheroembolism from severely diseased bypass grafts, which increase the risk of reoperation in general to approximately 2.0 to 3.5 times the risk of the first operation.<sup>244,363,367,368</sup> Emergency reoperative CABG has been reported to have a 17% operative mortality with a high rate of recurrent angina in operative survivors (74% at 24.9 months).<sup>245</sup>

**Patients Undergoing Cardiopulmonary Resuscitation**

Mortality rates in patients who have sustained cardiac arrest in the cardiac catheterization laboratory and who are not responsive to resuscitative measures are reported to be between 43% and 100%.<sup>369,370</sup> Rapid institution of extracorp-

**Table 7.** Clinical Profile of Mechanical Complications of Myocardial Infarction

Variable	VSD	Free Wall Rupture	Papillary Muscle Rupture
Age (mean, y)	63	69	65
Days post MI	3-5	3-6	3-5
Anterior MI	66%	50%	25%
New murmur	90%	25%	50%
Palpable thrill	Yes	No	Rare
Previous MI	25%	25%	30%
Echocardiographic findings			
Two-dimensional Doppler	Visualize defect Detect shunt	May have pericardial effusion	Flail or prolapsing leaflet Regurgitating jet in LA
PA catheterization	Oxygen step-up in Hi RV	Equalization of diastolic pressure	Prominent V wave in PCW tracing
Mortality			
Medical	90%	90%	90%
Surgical	50%	Case reports	40-90%

VSD indicates ventricular septal defect; MI, myocardial infarction; PA, pulmonary artery; LA, left atrium; RV, right ventricle; PCW, pulmonary capillary wedge. Modified with permission from Labovitz AJ, et al. Mechanical complications of acute myocardial infarction. *Cardiovasc Rev Rep*. 1984;5:948.

real cardiopulmonary bypass with adequate decompression of the heart can limit myocardial injury and provide other organ perfusion during the interval between cardiac arrest and myocardial reperfusion.<sup>371</sup> The decision to proceed with surgery in such cases requires careful consideration of whether the patient's condition is reversible.

#### Intraoperative Myocardial Protection in the Acutely Injured Heart

Acute ischemia following coronary occlusion results in structural, functional, and metabolic derangements not only in the ischemic myocardium but also in adjacent and remote myocardium. The use of intraoperative myocardial preservation strategies may limit and perhaps reverse ischemic injury in all areas.<sup>372</sup> Emergency CABG using substrate-enhanced reperfusate for cardiogenic shock has resulted in reversal of refractory LV dysfunction in 94% (75 of 80 patients)<sup>242</sup> and hospital survival in 91%. Other myocardial protection strategies that have been proposed to provide enhanced myocardial protection include normothermic blood cardioplegia without substrate enhancement<sup>373,374</sup> and hypothermic fibrillatory arrest without aortic cross-clamping and liberal use of preoperative intra-aortic balloon pumping.<sup>375,376</sup> The choice of intraoperative myocardial protection strategy should rest with the individual surgeon.

Previous reports of operation in the setting of acute MI have stressed the use of saphenous vein bypass grafts that permit antegrade delivery of cardioplegia solutions into the ischemic zone.<sup>377</sup> The use of retrograde (coronary sinus) cardioplegia that can perfuse the ischemic zone may permit greater use of internal mammary artery bypass grafts,<sup>378</sup> with the potential advantage of better long-term patency.

#### Management of Mechanical Defects After Acute Myocardial Infarction

##### Diagnosis

Mechanical defects can occur after acute MI and include acute mitral valve regurgitation, postinfarction VSD, LV free wall rupture, and LV aneurysm. Sudden and/or progressive hemodynamic deterioration with low cardiac output and/or pulmonary edema should lead to prompt consideration of these defects and rapid institution of diagnostic and therapeutic measures. The clinical and hemodynamic profiles of the common mechanical defects that occur after acute MI are summarized in Table 7.

These defects, when they occur, usually present within the first week after acute MI. On physical examination, the presence of a new cardiac murmur indicates the possibility of either VSD, mitral regurgitation, or, occasionally, ventricular rupture. A precise diagnosis can usually be established with transthoracic or transesophageal echocardiography.

Use of a balloon flotation catheter is helpful for both diagnosis and monitoring of therapy. With a VSD and left-to-right shunting, oxygen saturation will be higher in the pulmonary artery compared with the right atrium; in this instance, thermodilution cardiac output and pulmonary artery samples for mixed venous oxygen saturation will be falsely elevated. With acute mitral regurgitation, a large V wave will often be evident on the pulmonary artery wedge pressure tracing. With ventricular rupture and pericardial tamponade, equalization of diastolic pressure may be seen.

Coronary angiography can delineate the presence of surgically correctable coronary artery disease and should be done unless the patient is hemodynamically severely unstable from the mechanical defect alone. Cardiac catheterization may

better delineate the presence of a mechanical defect if other studies are not clear. Insertion of an intra-aortic balloon pump can help stabilize the patient as noted in "Hospital Management." Surgical consultation should be obtained when a mechanical defect is suspected so that preparations for surgical repair can be optimized. In general, prompt surgical repair is indicated, because medical treatment alone is associated with extremely high mortality.

### Acute Mitral Valve Regurgitation

With total rupture of a papillary muscle, medical treatment alone is associated with 75% mortality within the first 24 hours.<sup>379</sup> While emergency surgery is being arranged, the patient should receive nitroprusside to help lower pulmonary capillary pressures and improve peripheral perfusion. Although emergency mitral valve replacement is associated with relatively high mortality (27% to 55%), both overall mortality and subsequent ventricular function are improved, compared with medical therapy alone.<sup>380,381</sup> Delay in operation appears to increase the risk of further myocardial injury, other organ injury due to hypoperfusion, and subsequent death.<sup>380</sup> Repair of the mitral valve has also been reported in selected circumstances of both acute and chronic ischemic mitral insufficiency with good results.<sup>382</sup> When technically possible, the supporting structure of the mitral valve should be retained to more effectively preserve ventricular function.

### Postinfarction Ventricular Septal Defect

Increased frequency of acute rupture of the interventricular septum (VSD) as well as earlier presentation may be noted in patients who have undergone thrombolytic therapy.<sup>383</sup> Emergency surgical repair is indicated when pulmonary edema or cardiogenic shock is present; repair may be deferred in the hemodynamically stable patient. For patients with concomitant cardiogenic shock, only patients who underwent surgery within 48 hours survived.<sup>384</sup> Operative mortality is related to early operation (34% in the first week after infarction compared with 11% after the first week), but this is related to differences in the case mix; the presence of cardiogenic shock (39% compared with 8% without shock), site of infarction (32% inferior, 12% anterior), and age (25% older than 65 years, 17% for 65 years and younger).<sup>385</sup> Simultaneous CABG, if feasible, is indicated for associated significant coronary disease because long-term survival is improved.<sup>385,386</sup>

### Left Ventricular Free Wall Rupture

Surgery includes repair of the ventricle using a direct suture technique or patch to cover the ventricular perforation<sup>235</sup> in addition to CABG as needed. Alternatively, the use of cyanoacrylate glue has been described to hold the patch in place over necrotic myocardium.<sup>387</sup>

### Left Ventricular Aneurysm

Left ventricular aneurysm may be associated with refractory CHF, VT, or systemic embolization despite therapeutic anti-coagulation. Surgical techniques designed to retain ventricular geometry using endoventricular patches may maintain better

physiological function with lower (3.3% to 6.5%) mortality than earlier linear repair techniques (11.6% to 12.5% mortality).<sup>388,389</sup>

### Mechanical Support of the Failing Heart

*Intra-aortic balloon pump (IABP) support* improves diastolic coronary blood flow and reduces myocardial work. Its use is covered in detail in "Hospital Management."

*Circulatory support devices* include the use of prosthetic ventricles,<sup>390-392</sup> the LV turbine (Hemopump),<sup>393-395</sup> and percutaneous cardiopulmonary bypass circuits.<sup>396</sup> Each has been used in patients with cardiogenic shock after acute MI with improvement in other organ perfusion, in many cases as a bridge to definitive revascularization or cardiac transplantation. Total artificial heart implantation has also been used as a bridge to transplantation.<sup>397</sup> Success rates have varied and are generally correlated with the presence of correctable cardiac disease. Survival has been considered fair (from 20% to 33% at best) for this group of patients generally categorized as at very high risk for death if not otherwise treated. None of these devices has been used in a randomized fashion to assess their comparative efficacy in patients.

### Transplantation After Acute Myocardial Infarction

Cardiac transplantation has been reported for patients who sustained irreversible acute myocardial injury with no correctable lesion and who were otherwise acceptable candidates.<sup>398</sup> Of 15 patients reported, 9 had onset of shock within 3 days of onset of chest pain, and 6 had onset of shock within the first day. Cardiac assist devices were used in 6 patients as a bridge to transplantation. Early post-transplant mortality was 3 of 15 (20%).

### Relation Between Volume of Surgery and Outcome

Increasing attention is being directed at the better quality of surgical outcomes as a direct relation to a greater volume of surgical procedures per hospital<sup>399</sup> and per surgeon.<sup>400</sup> A retrospective review of 18 986 CABG procedures in 77 California hospitals suggested that higher volume hospitals had lower in-hospital mortality, particularly for "nonscheduled" surgery.<sup>401</sup> This suggests that patients with acute MI who might require emergency CABG should be directed to hospitals with higher surgical volume and acceptable surgical results.

### Minimum Operative Caseload

The ACC/AHA guidelines on coronary artery bypass graft surgery<sup>128</sup> suggest a minimum caseload of 200 to 300 open-heart operations per institution and 100 to 150 operations per surgeon, with the majority of operations done for coronary artery disease.

### Case Selection Concerns

As cardiac surgical programs and individual surgeons come under scrutiny with regard to operative mortality rates, con-

cern has been raised about the possibility that salvageable but high-risk patients may not be offered surgery. The committee believes strongly that patients should be offered surgical treatment if the treating team believes that the benefits outweigh the risks and that meaningful survival of the patient could result. Furthermore, appropriately validated risk-adjusted outcome measures should be used when evaluating the performance of an individual surgeon or surgical program.

## V. Rationale and Approach to Pharmacotherapy

### Nitroglycerin

#### Mechanism of Action

The primary action of nitrates is vasodilation, which is attributable primarily to nitrate-induced relaxation of vascular smooth muscle in veins, arteries, and arterioles. The metabolic conversion of organic nitrates to nitric oxide at or near the plasma membrane of the vascular smooth muscle cell represents the cellular basis for the vasodilatory action of these compounds.<sup>402</sup> Believed to be an endothelium-derived relaxing factor (EDRF), nitric oxide is an important endogenous modulator of vascular tone. Nitrate administration has been viewed as a means of providing an exogenous source of nitric oxide that may help replenish or restore the actions of EDRF, which are usually impaired in patients with coronary artery atherosclerosis.<sup>403</sup>

The reduction in right and left ventricular preload resulting from peripheral vasodilation, particularly in the splanchnic and mesenteric circulations, combined with afterload reduction resulting from arterial vasodilation, decreases cardiac work and lowers myocardial oxygen requirements.<sup>404</sup> As a consequence, the ratio of myocardial oxygen demand to myocardial oxygen supply improves, and myocardial ischemia is alleviated. Because of their hemodynamic profile, nitrates are particularly useful in patients with impaired LV systolic function or CHF. Additionally, both direct vasodilator effects of nitrates on the coronary bed and drug-induced prevention of episodic coronary artery vasoconstriction can increase global and regional myocardial blood flow, improving the subendocardial-epicardial blood flow ratio.<sup>405,406</sup> Enlargement of obstructive atherosclerotic lesions containing intact vascular smooth muscle can increase the caliber of some stenoses, improving coronary flow.<sup>407</sup> Nitrates also have been shown to dilate coronary collateral vessels, reverse vasoconstriction of small coronary arteries distal to a coronary obstruction, and reduce platelet aggregation.<sup>408</sup>

#### Pharmacokinetics and Dosage

As summarized by Abrams,<sup>409</sup> three nitrate compounds—nitroglycerin, isosorbide dinitrate (ISDN), and isosorbide-5-mononitrate (ISMN)—are available for clinical use in the United States. Nitroglycerin is characterized by a short half-life of only several minutes. Isosorbide dinitrate is an organic nitrate that is extensively metabolized in the liver to two active

metabolites, isosorbide-2- and ISMN. The half-life of ISDN ranges from 40 to 90 minutes. Isosorbide-5-mononitrate, the principal active metabolite of ISDN, is a synthetic nitrate approved by the Food and Drug Administration (FDA) in 1991. ISMN does not undergo hepatic metabolism and as a result is 100% bioavailable after oral dosing. Its half-life is 4 to 5 hours. Both ISDN and ISMN are available in sustained-release formulas. Nitroglycerin is the only nitrate available for intravenous use in the United States and the preparation of choice in the management of acute MI or unstable angina. Intravenous nitroglycerin can be successfully titrated by frequent measurement of blood pressure and heart rate. Although invasive hemodynamic monitoring is not mandatory, it may be preferable if high doses of vasodilating agents are required, blood pressure instability or hypotension ensues, or there is clinical doubt about the adequacy of LV filling pressure.<sup>410</sup>

When titrating intravenous nitroglycerin, begin with a bolus injection of 12.5 to 25.0 µg and a pump-controlled infusion of 10 to 20 µg/min, and increase the dosage by 5 to 10 µg every 5 to 10 minutes while carefully monitoring hemodynamic and clinical responses. Titration end points are control of clinical symptoms or decrease in mean arterial pressure of 10% in normotensive patients or 30% in hypertensive patients (but never a systolic pressure less than 90 mm Hg), an increase in heart rate greater than 10 bpm (but not exceeding 110 bpm), or a decrease in pulmonary artery end-diastolic pressure of 10% to 30%. Infusions are slowed or temporarily discontinued when mean blood pressure drops below 80 mm Hg or systolic blood pressure drops below 90 mm Hg. Although there is no absolute upper dosage limit, doses greater than 200 µg/min are associated with increased risk of hypotension, and alternative therapy should be considered.

The combination of intravenous nitroglycerin with a β-adrenergic blocking agent in appropriate patients is well tolerated and theoretically attractive because the risk of undesired tachycardia may be reduced. As nitrate tolerance develops, the infusion rate can be increased, but if it becomes necessary to administer more than 200 µg/min, another vasodilator such as nitroprusside or an ACE inhibitor should be substituted with the knowledge that effectiveness of nitroglycerin usually returns 12 hours after discontinuance.

#### Limitations and Adverse Effects

In addition to frequently causing headaches, nitroglycerin may also aggravate hypoxemia by increasing ventilation-perfusion mismatch. The most serious side effect is inadvertent systemic hypotension, which may result in reflex tachycardia and worsening myocardial ischemia. Nitroglycerin should be carefully titrated in patients with inferior wall MI because of its frequent association with RV infarction. Such patients are especially dependent on adequate RV preload to maintain cardiac output and can experience profound hypotension during nitrate administration.<sup>73</sup> When nitroglycerin administration results in bradycardia and hypotension, discontinuation

of the drug, leg elevation, rapid fluid administration, and atropine are appropriate.

Continuation of the anti-ischemic effects of organic nitrates with repeated dosing is the major limitation in use of these drugs. Nitroglycerin tolerance is a complex multifactorial phenomenon that may partially be explained by a relative depletion of sulphydryl groups required for conversion of organic nitrates to nitric oxide.<sup>411</sup> More recently it has been suggested that enhanced vascular superoxide production plays an important role in this phenomenon.<sup>412</sup> It is now clear that intermittent dosing regimens that allow for a drug-free interval represent the only practical and effective strategy for avoiding nitrate tolerance. When ISDN is used, anti-ischemic activity is more likely to be maintained with a dosing schedule of 2 or 3 times daily. FDA labeling now indicates a dose-free interval of 14 hours is required to avoid tolerance. An asymmetric ISMN dosing regimen, with administration at 8 AM and 3 PM, has been shown to sustain the anti-ischemic effects of the short-acting preparation of this agent.<sup>413</sup> When using intravenous nitroglycerin for 24 to 48 hours continuously in the early stages of acute MI, it is well to note that drug tolerance is not usually recognized at the bedside. If the desired nitrate effects are lost during this period, it is appropriate to increase the intravenous infusion dose.

Physicians need to be aware of a potential drug interaction between heparin and intravenous nitroglycerin, although as yet unresolved, because these agents are frequently administered at the same time. Several reports have suggested that intravenous nitroglycerin may interfere with the actions of heparin on the activated partial thromboplastin and prothrombin time, thereby decreasing sensitivity to heparin.<sup>414-415a</sup> Thus, in addition to requiring increased heparin dosage to achieve a desired anticoagulation end point, patients may be at greater risk for bleeding when nitroglycerin is discontinued and infusion of heparin continues.

### Clinical Trials

There is experimental and clinical evidence that intravenous nitroglycerin may reduce infarct size and improve regional myocardial function.<sup>416-417</sup> It has also been suggested that nitroglycerin may prevent LV remodeling that frequently occurs after a large transmural MI.<sup>417</sup> In the prereperfusion era a number of small studies demonstrated an improvement in mortality and major cardiovascular morbidity following early administration of intravenous nitroglycerin. A meta-analysis of these earlier trials involving 2042 patients suggested that nitrates reduced the odds of death after acute MI by 35% (95% CI, 28 to 49%;  $P < .001$ ).<sup>418</sup> Similar analyses involving the use of oral nitrates in fewer patients estimated a treatment effect of about 20%, but this was not statistically significant, and the greatest reduction in mortality occurred during the first week or so of follow-up.<sup>418,419</sup>

The use of nitrate therapy was investigated in the context of routine use of thrombolytic therapy and aspirin with short-term mortality as the primary end point in two recently completed large trials. The GISSI-3 trial<sup>420</sup> randomly assigned

19 394 patients to a 24-hour infusion of nitroglycerin (beginning within 24 hours of onset of pain), followed by topical nitroglycerin (10 mg daily) for 6 weeks (with patch removed at bedtime, allowing a 10-hour nitrate-free interval to avoid tolerance), or control. Approximately 50% of patients in the control group received nitrates on the first day or two at the discretion of their physician. There was an insignificant reduction in mortality at 6 weeks in the group randomly assigned to nitrate therapy alone, compared with the control group (6.52% versus 6.92%, respectively). GISSI-3 evaluated lisinopril in a similar fashion; 6-week mortality was reduced slightly. At both 6-week and at 6-month follow-up, the combined use of lisinopril and nitrates led to a greater reduction in mortality when compared with the group that received no nitrate therapy or lisinopril alone. The other large trial, ISIS-4,<sup>421</sup> compared 28-day treatment of controlled-release oral isosorbide mononitrate with placebo control (as well as intravenous magnesium sulfate versus control and the ACE inhibitor captopril versus placebo control) in a  $2 \times 2 \times 2$  factorial design in 58 050 patients with suspected MI. Nitrate therapy in ISIS-4 was associated with a small, nonsignificant reduction in 35-day mortality compared with the control group (7.34% versus 7.54%) in the overall comparison. All subgroups examined, including those not receiving short-term nonstudy intravenous or oral nitrates at entry, failed to demonstrate a significant mortality benefit with nitrate use. In both GISSI-3 and ISIS-4, the power to detect potential beneficial effects of routine nitrate therapy was reduced by the extensive early use (greater than 50%) of nontrial nitrate in the control subjects. When data from all randomized control trials of nitrate use in the management of acute MI are combined, there is a small relative reduction in mortality that is statistically significant ( $5.5\% \pm 2.6\%$ ;  $2P = .03$ ),<sup>421</sup> which represents approximately 4 lives saved per 1000 treated.

The totality of evidence from all pertinent randomized clinical trials does not support routine use of long-term nitrate therapy in patients with uncomplicated acute MI. However, it is prudent to use intravenous nitroglycerin for the first 24 to 48 hours in patients with acute MI and recurrent ischemia, CHF, or management of hypertension. It should be continued orally or topically in patients with CHF and large transmural MIs as well. Intravenous administration is recommended in the early stage of acute MI because of its onset of action, ease of titration, and the opportunity for prompt termination in the event of side effects.

### Aspirin and Other Platelet-Active Drugs

Platelets and thrombosis play important roles in the pathogenesis of acute coronary artery syndromes, and the role of antiplatelet agents has been recently reviewed in two publications, the AHA statement "Aspirin as a Therapeutic Agent in Cardiovascular Disease"<sup>422</sup> and the fourth American College of Chest Physicians (ACCP) Consensus Conference on Anti-thrombotic Therapy.<sup>423</sup>

### Mechanism of Action of Aspirin

In platelets, aspirin prevents formation of thromboxane A<sub>2</sub>, a substance that induces platelet aggregation.<sup>424-426</sup> Because platelets are unable to generate new cyclo-oxygenase enzyme inhibition lasts for the life of the cell, or about 10 days. In vascular endothelial cells aspirin prevents the synthesis of prostacyclin, which inhibits platelet aggregation.<sup>427</sup> Endothelial cells can recover cyclo-oxygenase synthesis so that the inhibitory effects of aspirin may be of shorter duration than with platelets.<sup>428,429</sup>

### Aspirin in Prevention of Thrombotic Complications of Atherosclerosis

As summarized in the fourth ACCP Consensus Conference on Antithrombotic Therapy<sup>423</sup>:

In the recently reported overview of the Antiplatelet Trialists' Collaboration that involved 145 trials, the antiplatelet therapy (mainly aspirin) of 70 000 high-risk patients and 30 000 low-risk patients was found to be protective against vascular events among the following patients: (1) patients with acute MI, 10% versus 14% (at 1 month); (2) a history of MI, 13% versus 17% (2-year follow-up); (3) a history of stroke or transient cerebral ischemia, 18% versus 22% (3-year follow-up); (4) unstable angina, 9% versus 14% (6-month follow-up); and (5) other miscellaneous vascular diseases, 6% versus 8% (1-year follow-up).

When all high-risk patients are considered together, there is about a 30% reduction in nonfatal MI, a 30% reduction in nonfatal stroke, and a 17% reduction in vascular death. For patients with prior infarction or stroke, aspirin is estimated to prevent between 35 and 40 events per 1000 patients treated. In contrast, when used in asymptomatic men, aspirin prevents only 4 events per 1000 subjects treated.

### Aspirin: Risk of Hemorrhagic Stroke

A small increase in incidence of stroke in healthy men treated with aspirin was reported in both the American Physician and the British Doctors primary prevention studies.<sup>430</sup> However, there has been no evidence of an increased incidence of stroke in studies in which aspirin was used for secondary prevention of coronary artery disease. These secondary prevention trials clearly indicate that in patients with clinical manifestations of atherosclerotic disease, aspirin reduces risk of stroke. It is likely that as a consequence of its antihemostatic effect, aspirin produces a small increase in risk of cerebral hemorrhage, which is masked by the beneficial effects of aspirin in patients with an increased risk for thromboembolic stroke but becomes manifest in healthy individuals at very low risk for this event.

### Aspirin: Side Effects and Dosage

The side effects of aspirin are mainly gastrointestinal and dose related.<sup>431</sup> Gastric side effects may also be reduced by administration of diluted solutions of aspirin,<sup>432</sup> treatment with cimetidine,<sup>433</sup> antacids,<sup>432,434</sup> or use of enteric-coated or buffered aspirin.<sup>435,436</sup>

Aspirin should be avoided in those with a known hypersensitivity and used cautiously in those with blood dyscrasias or severe hepatic disease. If the patient has a history of bleeding peptic ulcers, rectal aspirin suppositories can be used safely. Another potentially deleterious effect of aspirin is risk of bleeding from surgical sites. Patients who received aspirin in the Veterans Administration Cooperative Study<sup>437</sup> were noted to have significantly increased postoperative chest drainage and reoperation for bleeding (6.5% for aspirin groups compared with 1.7% for nonaspirin groups,  $P < .01$ ). Others have noted that preoperative aspirin use has been associated with increased postoperative chest drainage but not an increased rate of reoperation for bleeding.<sup>438,439</sup> In another Veterans Administration Cooperative Study,<sup>440</sup> starting aspirin 6 hours after surgery conferred the benefits of improved saphenous vein bypass graft patency without the increased postoperative bleeding seen with preoperative administration of aspirin.

Aspirin is an effective antithrombotic agent in doses between 75 mg and 1.2 g/d. It is also possible that 30 mg/d is effective. There is no evidence that low doses are either more or less effective than high doses when used over the long term, although doses less than 160 mg/d may not be effective acutely.

### Ticlopidine

Ticlopidine is an antiplatelet drug with a different mechanism of action than aspirin. It inhibits platelet aggregation induced by a variety of agonists, including adenosine diphosphate, possibly by altering the platelet membrane and blocking the interaction between fibrinogen and its membrane glycoprotein receptor, GPIIb/IIIa.<sup>441</sup> The inhibitory effect of ticlopidine is delayed for 24 to 48 hours after its administration; thus, ticlopidine may not be useful when a rapid antiplatelet effect is required.

Ticlopidine has been shown to be more effective than a control therapy in reducing vascular death and MI in patients with unstable angina.<sup>441</sup> The most serious side effect of its use is reversible neutropenia, which has only been observed when treatment is continued for more than 2 weeks. It has been approved for clinical use in patients with cerebral ischemia when aspirin has failed, cannot be tolerated, or is contraindicated.

### Rationale for Thrombolytic Therapy

#### Background

Herrick<sup>442</sup> in the United States and Obrastzow and Straschesko<sup>443</sup> in the Soviet Union first described the clinical features of sudden obstruction of the coronary arteries more than 80 years ago. However, the pathophysiology of acute MI and specifically the role of coronary thrombosis were controversial until the early 1980s. The landmark study of DeWood and colleagues,<sup>440</sup> published in 1980, demonstrated complete, presumably thrombotic occlusion of the infarct-related artery in 87% of patients with MI and ST elevation studied angiographically within 4 hours of onset of symptoms and in 65%

**Table 8.** Comparison of US FDA-Approved Thrombolytic Agents

	SK	APSAC	TPA
Dose	1.5 million U in 30-60 min	30 mg in 5 min	100 mg in 90 min*
Circulating half-life (min)	20	100	6
Antigenic	Yes	Yes	No
Allergic reactions	Yes	Yes	No
Systemic fibrinogen depletion	Severe	Severe	Moderate
Intracerebral hemorrhage	≈0.3%	≈0.6%	≈0.6%
Recanalization rate, 90 min†	≈40%	≈63%	≈79%
Lives saved per 100 treated	≈2.5	≈2.5	≈3.5‡
Cost per dose (approx US dollars)	290	1700	2200

US FDA indicates United States Food and Drug Administration; SK, streptokinase; APSAC, anisoylated plasminogen streptokinase activator complex; TPA, tissue plasminogen activator; approx, approximately. \*Accelerated TPA given as follows: 15 mg bolus, then 0.75 mg/kg over 30 min (maximum, 50 mg), then 0.50 mg/kg over 60 min (maximum, 35 mg). †Based on published data and assuming that 20% of arteries are open before therapy. ‡Based on the finding from the GUSTO (Global Utilization of Streptokinase and TPA for Occluded Arteries) trial that accelerated TPA saves 1 more additional life per 100 treated than does SK. Adapted from Table 3.1 and reprinted from *Management of Acute Myocardial Infarction* (Julian D, Braunwald E, eds). Martin GV, Kennedy JW. Choice of thrombolytic agent, p 73, 1994. By permission of the publisher. WB Saunders Co Ltd, London.

studied between 12 and 24 hours. The subsequent demonstration of intraluminal thrombus at the time of emergency coronary surgery<sup>440</sup> and the demonstration of infarct-related artery recanalization by intracoronary thrombolytic therapy<sup>443-445</sup> led to the unequivocal role of intracoronary thrombus in acute coronary occlusion. Subsequent pathological and angioscopic observations led to the concept that fissuring or rupture of a vulnerable atherosclerotic plaque was the initiating mechanism of coronary occlusion as a result of coronary spasm, intraplaque hemorrhage, and luminal thrombosis.<sup>446-448</sup> A second premise supporting large trials of thrombolytic therapy in acute MI was the observation in animal models and early clinical studies that reperfusion could lead to myocardial salvage and improved outcome, but that benefit was time dependent. Reimer, Jennings, and coworkers<sup>449</sup> showed that coronary artery occlusion in an animal model led to MI that proceeded in a "wavefront" from subendocardium to subepicardium, beginning within 20 minutes and evolving to more than 70% transmural necrosis in 6 hours, with a small amount of additional necrosis between 6 and 24 hours. Of note, reestablishment of coronary flow within 2 hours resulted in substantial myocardial salvage and functional recovery of the ischemic myocardium, whereas reperfusion as late as 6 hours resulted in limited, subepicardial salvage. Subsequent early controlled clinical trials demonstrated the potential for functional and mortality benefit, but only if therapy was given early and reperfusion resulted.<sup>450-453</sup>

Clinical use of intravenous preparations containing streptokinase for acute MI dates back four decades.<sup>454,455</sup> However, contemporary interest in intravenous thrombolytic therapy was reawakened with reports in the mid 1980s of its feasibility and comparability to intracoronary therapy.<sup>456-458</sup> Subsequent clinical studies and practical application of thrombolytic therapy has focused on the more broadly and rapidly applicable intravenous application of thrombolytic agents.

### Thrombolytic Agents: General Mechanisms of Action and Pharmacological Properties

Recognition that acute coronary thrombosis is primary to the pathogenesis of acute MI led to the consideration of plasminogen activators as a preferred therapeutic approach to achieving rapid thrombolysis. All of the thrombolytic (fibrinolytic) agents currently available and under investigation are plasminogen activators.<sup>459</sup> They all work enzymatically, directly or indirectly, to convert the single-chain plasminogen molecule to the double-chain plasmin (which has potent intrinsic fibrinolytic activity) by splitting a single bond at the arginine 560-valine 561 site, exposing the active enzymatic center of plasmin.

Aside from this similarity, however, there are many differences among these agents in dose, circulating half-life, "fibrin-specificity" (relative activity against clot-bound fibrin versus circulating fibrinogen), rates of coronary recanalization, risks of ICH, and cost. Some comparative features of the FDA-approved thrombolytic agents for intravenous therapy (streptokinase, anistreplase), and the tissue plasminogen activator alteplase are presented in Table 8. Streptokinase and urokinase are approved for intracoronary use, but this route of administration for acute MI is now virtually obsolete. In addition, newer agents are being developed (eg, prourokinase, staphylokinase, and various mutant plasminogen activators). Recent trials with alteplase have used an accelerated or frontloaded dosing regimen (dose given over 90 minutes rather than 3 hours). Because the accelerated regimen leads to greater early patency rates without an increase in hemorrhagic risk, it has become the preferred method of administration.

### Efficacy of Intravenous Thrombolytic Therapy in Acute Myocardial Infarction

It has now been well established that thrombolytic therapy provides a survival benefit for patients with acute MI, based on

large, well-controlled clinical trials. Benefit has been shown individually for therapy with streptokinase, anistreplase, and alteplase.<sup>28,29,460,461</sup> In an overview of the nine controlled randomized trials involving more than 1000 patients, a highly significant ( $P<.00001$ ) 18% proportional reduction in mortality was observed, corresponding to the avoidance of 18 deaths per 1000 patients treated.<sup>27</sup> Furthermore, the largest of these studies (ISIS-2, more than 17 000 patients), showed that when aspirin was combined with streptokinase and treatment was given within 4 hours of onset of symptoms, an odds reduction in mortality of 53% was achieved (control, 13.1%; streptokinase plus aspirin, 6.4%) ( $P<.0001$ ).<sup>29</sup> Information from both animal studies as well as clinical trials has provided strong support for the concept that achievement of early, complete, and sustained coronary patency is primarily responsible for benefit of treatment.<sup>30</sup> Mechanisms of benefit include favorable effects on myocardial salvage as well as postinfarction remodeling.

### Benefits of Thrombolytic Therapy in Specific Patient Subgroups

The overview of thrombolysis trials shows that thrombolytic therapy is clearly beneficial in the vast majority of patients. Differences in outcome in subgroups in clinical trials should be interpreted more cautiously than overall differences in outcome with therapy, given the problems of multiple comparisons and chance deviations from the mean. Sometimes differences in degree (and rarely, direction) of benefit appear among some subgroups, and when these are replicated in independent trials and supported by a clear pathophysiological rationale may reflect valid differences. Implications of overall and subgroup results from the overview of the major randomized, controlled clinical trials<sup>27</sup> for use of thrombolytic therapy in acute MI are presented in "Initial Recognition and Management in the Emergency Department."

### Comparative Thrombolytic Efficacy

Since publication of the first guidelines for the early management of patients with acute myocardial infarction,<sup>1</sup> results of important trials comparing thrombolytic regimens directly have been published, evaluating relative rates of coronary patency, functional benefit, and survival. In two large mortality trials (GISSI-2/International<sup>462</sup> and ISIS-3<sup>463</sup>), mortality rates at 4 to 5 weeks were similar (GISSI-2/International: TPA [duteplase]=8.9%, streptokinase=8.5%; ISIS-3: alteplase=10.3%, streptokinase=10.6%, anistreplase=10.5%). In these studies conjunctive antithrombotic therapy included aspirin in all patients (160 to 325 mg on admission and daily) and subcutaneous heparin in half (12 500 U twice a day, beginning 4 to 12 hours after thrombolytic therapy). At the time, intravenous heparin was not used in either of these studies because of concerns about increasing the incidence of ICH. The specific failure to use intravenous heparin with TPA in these trials has been the source of some criticism. The GUSTO trial subsequently tested four thrombolytic regimens among 41 021 patients.<sup>228</sup> Alteplase was given in an accelerated dose

regimen to further improve early patency rates and concomitant heparin administered intravenously to maintain patency. Other regimens included streptokinase with subcutaneous or intravenous heparin and a combination of alteplase and streptokinase. Thirty-day mortality was lower with alteplase (6.3%) than streptokinase and subcutaneous heparin (7.2%), streptokinase and intravenous heparin (7.4%), and combined streptokinase and alteplase plus intravenous heparin therapies (7.0%). Differences were highly significant, although proportionately modest, when accelerated alteplase was compared with combined streptokinase groups (14% mortality reduction,  $P=.001$ ). There was a significant excess of hemorrhagic stroke for accelerated alteplase ( $P=.03$ ) and the combination strategy ( $P<.001$ ), compared with streptokinase only. However, net benefit was still achieved with alteplase compared with streptokinase, with 9 fewer deaths or disabling strokes per 1000 patients treated. Other complications of acute MI were generally less frequent with alteplase, including allergic reactions, heart failure, cardiogenic shock, and atrial and ventricular arrhythmias.

Other conclusions drawn from GUSTO are (1) intravenous heparin provides no added benefit over aspirin and subcutaneous heparin when given with streptokinase and in addition increases bleeding risk (the power of this comparison, however, was markedly reduced by the fact that 36% of patients randomly assigned to receive subcutaneous heparin also received intravenous heparin); (2) combination therapy increases bleeding risk (relative to alteplase with intravenous heparin) and provides less benefit; and (3) although the rationale for use of intravenous heparin with alteplase appears sound, other factors, specifically, earlier time to therapy, frontloading alteplase, and requiring ST elevation on entry ECG, likely explain much of the difference in results between GUSTO and ISIS-3.<sup>464</sup> The mechanism of improved benefit with alteplase was assessed in the GUSTO angiographic substudy, which found differences in early (90-minute) patency among regimens (81%, 56%, 61%, 73%) for alteplase, streptokinase–subcutaneous heparin, streptokinase–intravenous heparin, and combination regimens, respectively.<sup>465</sup> These differences in patency in the angiographic substudy closely predicted survival outcomes among the four strategies when applied to the main trial results<sup>466</sup> and furnish a biological explanation for mortality differences among regimens. The data, coupled with that of additional, independent comparisons showing superior outcomes with accelerated alteplase compared with anistreplases,<sup>467,468</sup> provide a strong impetus for early and complete restoration of infarct artery perfusion as an essential goal of thrombolytic therapy.

### Considerations in Selecting Thrombolytic Regimens

GUSTO<sup>228</sup> and other recent studies<sup>467,468</sup> suggest that accelerated alteplase with intravenous heparin is currently the most effective therapy for achieving early coronary reperfusion and its associated survival benefits but is also substantially more expensive and carries a greater risk of ICH. Thus, the cost-benefit ratio is greatest in patients presenting early after

symptom onset with a large area of injury (eg, anterior acute MI) and at low risk of ICH. In groups with a smaller potential for survival benefit and a greater risk for ICH, streptokinase appears to be the agent of choice, particularly in view of the cost. Other promising thrombolytic agents are under investigation (eg, prourokinase, reteplase, staphylokinase, TNK-plasminogen activator).

A number of proposals for selection of thrombolytic regimens after GUSTO have been suggested.<sup>36,469-471</sup> Additional considerations include avoiding reuse of streptokinase or anistreplase for at least 2 years (preferably indefinitely) because of a high prevalence of potentially neutralizing antibody titers. Alternatively, Simoons<sup>470</sup> has proposed considering primary PTCA for those at highest risk (about 10% of patients), alteplase for those at moderate to high risk (40%), streptokinase for those at low to moderate risk (40%), and no lytic therapy for those at lowest risk (10%). All of these recommendations await prospective testing.

#### Current Use Rates for Thrombolytic Therapy

The industry-sponsored National Registry of Myocardial Infarction tracks the use of thrombolytic therapy in the United States and has enrolled 220 171 patients treated at 1370 US hospitals during its second phase (NRMI 2) from June 1994 through December 1995. Overall, 37.2% received reperfusion therapy (83% thrombolysis, 15.4% primary angioplasty, 1.4% immediate CABG) (written communication, W. J. Rogers, June 1996). Among a subset of patients presenting with ST elevation or LBBB within 12 hours of symptom onset ( $n=64\,211$ ), the use of reperfusion therapy was 70%, with 8.2% of the cohort receiving primary PTCA.<sup>472</sup>

Because many patients have contraindications or other exclusions for fibrinolytic agents, it has been difficult to ascertain the proportion of patients with ST elevation who fail to receive fibrinolytic therapy that actually should have received such therapy.<sup>472a</sup> Critical to any such assessment of appropriateness of care, however, is whether the diagnosis of acute MI was suspected on entry into the healthcare system or was an "outcomes" diagnosis made after 12 to 24 hours in the hospital or at some later point in time before hospital discharge. Experience to date suggests that in patients younger than 65 years, overall usage of thrombolytic therapy ranges between 40% and 50% (as high as 70% to 75% for patients with ST-elevation MI). In those older than 65, the overall use rate is below 20% and should be higher. Some increase in use rates probably can be achieved, but contraindications prohibit a vast increase in use rates.

#### Antiplatelets/Anticoagulants

Once fissuring of an atherosclerotic plaque has occurred, whether an epicardial coronary vessel becomes totally occluded, develops a more severe, flow-limiting stenosis, or heals without incident depends to a large extent on the degree to which thrombus propagates in the vessel lumen. As previously discussed, platelet activation and aggregation are crucial ele-

**Table 9. Heparin Adjustment Nomogram for Standard Laboratory Reagents With a Mean Control aPTT of 26-36 s**

aPTT (s)	Bolus Dose (U)	Stop Infusion (min)	Rate Change (mL/h)	Repeat aPTT
<40	3000	0	+2	6 h
40-49	0	0	+1	6 h
50-75	0	0	0 (no change)	Next AM
76-85	0	0	-1	Next AM
86-100	0	30	-2	6 h
101-150	0	60	-3	6 h
>150	0	60	-6	6 h

aPTT indicates activated partial thromboplastin time. Heparin infusion concentration = 50 U/mL. Target aPTT = 50-75 s. For aPTTs obtained before 12 h after initiation of thrombolytic therapy: 1. Do not discontinue or decrease infusion unless significant bleeding or aPTT >150 s. 2. Adjust infusion upward if aPTT <50 s. For aPTTs obtained ≥12 h after initiation of thrombolytic therapy, use entire nomogram: Deliver bolus, stop infusion, and/or change rate of infusion based on aPTT, as noted on appropriate line of nomogram. Adapted with permission from Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Piller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest*. 1995;108:258S-275S.

ments of the process, but the balance between activation of the coagulation cascade and its inhibition is also critical. The process by which a thrombus is formed is complex, and our understanding of it continues to evolve,<sup>473</sup> but much of the therapeutic effort has focused on inhibiting thrombin and thereby preventing conversion of fibrinogen to fibrin. In addition to having a primary role in this initial process of coronary thrombosis, thrombin also is an important platelet activator; activation of platelets by thrombin is not inhibited by aspirin. Another reason that thrombin is considered critical is that active thrombin becomes bound to a developing clot, and as the clot lyses, either pharmacologically or through endogenous means, the "clot-bound" thrombin can convert fibrinogen to fibrin as it is exposed to the circulating blood.

#### Heparin

##### Recommendations

###### *Class I*

1. Patients undergoing percutaneous or surgical revascularization.

*Comment:* For PTCA, monitoring of activated clotting time (ACT) is recommended, with a goal of 300 to 350 seconds during the procedure.

###### *Class IIa*

1. Intravenously in patients undergoing reperfusion therapy with alteplase.

*Comment:* The recommended regimen is 70 U/kg as a bolus at initiation of alteplase infusion, then an initial maintenance dose of approximately 15 µg/kg per hour, adjusted to maintain aPTT at 1.5 to 2.0 times control (50 to 75 seconds) for 48 hours (Table 9). Continuation of heparin infusion beyond 48 hours should be restricted to patients at high risk for systemic or venous thromboembolism.

**2. Subcutaneously (7500 U twice daily) (intravenous heparin is an acceptable alternative) in all patients not treated with thrombolytic therapy who do not have a contraindication to heparin. In patients who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, or known LV thrombus), intravenous heparin is preferred.**

**3. Intravenously in patients treated with nonselective thrombolytic agents (streptokinase, anistreplase, urokinase) who are at high risk for systemic emboli (large or anterior MI, AF, previous embolus, or known LV thrombus).**

*Comment: It is recommended that heparin be withheld for 4 hours and that aPTT testing begin at that time. Heparin should be started when aPTT returns to less than two times control (about 70 seconds), then infused to keep aPTT 1.5 to 2.0 times control (initial infusion rate about 1000 U/h). After 48 hours, a change to subcutaneous heparin, warfarin, or aspirin alone should be considered.*

#### **Class IIb**

**1. Patients treated with nonselective thrombolytic agents, not at high risk, subcutaneous heparin, 7500 U to 12 500 U twice a day until completely ambulatory.**

#### **Class III**

**1. Routine intravenous heparin within 6 hours to patients receiving a nonselective fibrinolytic agent (streptokinase, anistreplase, urokinase) who are not at high risk for systemic embolism.**

Heparin has been available as an anticoagulant for many years; it was initially described in 1916. The pharmacological entity consists of a mixture of molecules with molecular weights varying between 5000 and 20 000, with different-size molecules having different effects on the coagulation system. After forming a complex with antithrombin III (AT-III), the heparin-AT-III complex has the ability to inactivate both thrombin and activated factor X. When a dose of heparin is given, the actual measured effect on coagulation is modulated by a number of factors, including the particular admixture of heparin molecules in the dose, circulating levels of AT-III, availability of platelet factor IV and other plasma proteins that inactivate heparin, and the ability of heparin to reach thrombin bound to clot. The heparin-AT-III complex is quite large and generally does not appear to be effective against clot-bound thrombin.

In patients who will not be given thrombolytic therapy, there is little evidence about the benefit of heparin in the modern era, in which aspirin,  $\beta$ -adrenoceptor blockers, nitrates, and ACE inhibitors are routinely available. Nevertheless, the best available data emanate from a series of randomized clinical trials performed before the reperfusion era. A systematic overview of these studies demonstrated a 17% reduction in mortality and a 22% reduction in risk of reinfarction with heparin.<sup>474</sup> The control groups in these trials were not treated with other therapies, particularly aspirin, that are now considered routine. Notwithstanding, it is primarily these randomized data from an earlier era that support the recom-

mendation to use heparin in patients not treated with thrombolytic therapy.

In patients who are treated with thrombolytic therapy, recommendations for heparin therapy depend on the thrombolytic agent chosen. Streptokinase, anistreplase, and urokinase are nonspecific fibrinolytic agents that produce systemic breakdown of the coagulation system, including depletion of factors V and VIII and massive production of fibrin(ogen) degradation products, themselves anticoagulants. From this perspective, the need for conjunctive systemic anticoagulation with these agents is conceptually less. In comparison, relatively fibrin-specific agents, including alteplase and newer agents such as reteplase, produce a variable effect on the systemic coagulation system, and in many patients very little breakdown of fibrinogen or depletion of coagulation factors is evident.<sup>475,476</sup>

More than 60 000 patients were enrolled in the randomized ISIS-3<sup>463</sup> and GISSI-2/International<sup>477</sup> trials comparing subcutaneous heparin with no routine heparin in conjunction with streptokinase, anistreplase, and alteplase. During the period in which heparin was given, a small reduction in mortality (4 to 5 lives per 1000 treated) was observed in ISIS-3; however, by 30 days the 2 to 3 lives saved per 1000 treated was no longer statistically significant. A small excess rate of hemorrhagic stroke (1 to 2 per 1000 treated patients) was observed together with a larger excess in systemic bleeding (3 to 5 per 1000 patients), although total stroke rate was not significantly increased. In the GUSTO-I trial,<sup>478</sup> more than 20 000 patients treated with streptokinase were randomly assigned to routine intravenous heparin versus routine subcutaneous heparin. No significant differences were observed in death, reinfarction, or nonhemorrhagic stroke rates, while excess rates of systemic bleeding and hemorrhagic strokes (trend) were observed in the intravenous heparin group.

Several angiographic studies have evaluated coronary perfusion as a function of heparin therapy.<sup>478,479</sup> Two trials have shown more rapid resolution of ST-segment elevation in patients treated with intravenous heparin immediately at the time of streptokinase infusion compared with intravenous heparin started at a later time.<sup>478,479</sup> The OSIRIS study, however, showed no difference in perfusion at 24 hours or in clinical outcomes in the two groups. In the GUSTO-I angiographic substudy, patients treated with intravenous heparin had an 88% patency rate at 5 to 7 days compared with 72% in patients treated with subcutaneous heparin ( $P < .05$ ), although less reinfarction occurred in the subcutaneous heparin group (3.4% versus 4.0%,  $P < .05$ ). A small group of patients were randomly assigned to anistreplase with or without intravenous heparin in the DUCSS-1 study,<sup>480</sup> and no differences in clinical end points were observed, other than a higher rate of bleeding in heparin-treated patients. Viewing these studies as a whole, intravenous heparin appears to have no advantage over subcutaneous heparin when used with a nonspecific thrombolytic agent, and the evidence for use of subcutaneous heparin is equivocal.<sup>481</sup>

The occurrence of a large, anterior infarction, documenta-

tion of thrombus in the left ventricle by echocardiography, history of a previous embolic event, and AF have been associated with a high risk of embolic stroke. Although no randomized trial evidence exists to demonstrate a definite benefit specific to this group, some empirical evidence exists that the risk of systemic emboli in the general population of MI patients can be reduced by early initiation of heparin.<sup>482</sup> In the SCATI trial patients were randomly assigned to a 2000 IU bolus of heparin followed by 12 500 IU subcutaneously twice a day or to placebo. In the subgroup also treated with streptokinase, aspirin was withheld. In-hospital mortality was 4.6% in the heparin group and 8.8% in the control group, and a reduction in stroke was observed. Therefore, heparin is recommended for these patients at high risk of systemic arterial emboli, regardless of the thrombolytic agent given.

When alteplase is chosen as the thrombolytic agent, the empirical information to confirm the pathophysiological reasoning discussed above is primarily inferential. In a series of angiographic trials,<sup>483-485</sup> intravenous heparin has been shown to lead to higher rates of infarct-related artery perfusion in conjunction with alteplase. When aPTT has been evaluated, a direct relation between duration of aPTT and the likelihood of infarct-related artery perfusion has been observed.<sup>484,485</sup> A recent overview<sup>486</sup> points out, however, that the effects of intravenous heparin on clinical outcomes from these studies are not as convincing; a significant increase in the rate of bleeding and nonsignificant increases in rates of reinfarction and hemorrhagic and nonhemorrhagic stroke are evident.<sup>486</sup> These negative findings are tempered by a point estimate of an 18% reduction in mortality with broad confidence limits. Until the uncertainty is resolved, it seems judicious to use heparin for at least 48 hours with alteplase and to target the aPTT to a 50- to 75-second range.

When primary angioplasty is chosen as the route of reperfusion, high-dose heparin therapy is recommended. This recommendation does not come specifically from empirical data in the acute MI setting but from general observations in the setting of angioplasty that an ACT of at least 300 to 350 seconds is associated with a lower rate of complications than lower ACT values.<sup>487,488</sup>

Very recently abciximab, a Fab fragment of humanized monoclonal antibody to the glycoprotein IIb/IIIa receptor on the platelet surface, has been demonstrated to reduce the risk of adverse outcomes significantly, both at 30 days<sup>489</sup> and at 6 months<sup>490</sup> after high-risk percutaneous intervention.<sup>489,491</sup> Benefit, however, was accomplished at the price of an increase in major bleeding from 13% to 24%. Abciximab, like experimental IIb/IIIa antagonists, increases the ACT measurement with a given dose of heparin by an average of 35 seconds.<sup>491</sup> A recent trial with abciximab compared this agent with placebo in the context of standard heparin dosing in the placebo group and two heparin regimens with abciximab: a weight-adjusted standard dose and a lower dose aimed at achieving an ACT of 150 to 300 seconds during routine as well as high-risk percutaneous procedures.<sup>492</sup> The trial was terminated early when an interim analysis showed a combined rate of death and nonfatal

MI of 8.1% in the placebo group, 3.6% in the weight-adjusted heparin arm, and 2.6% in the low-dose heparin arm. A trend toward less bleeding in the low-dose heparin arm compared with the placebo arm was also reported. A third trial evaluating abciximab in the treatment of refractory unstable angina also was stopped early because of a 40% reduction in the composite end point of death, MI, or need for repeat revascularization.<sup>492,493</sup>

The dose of heparin in the thrombolytic-treated patient remains somewhat controversial. Based on the infarct-related artery perfusion results described above, it would be reasonable to recommend an aPTT value more than threefold higher than the median control value. However, recent information strongly supports a lower aPTT because death, stroke, reinfarction, and bleeding were found to be lowest in the aPTT range of 50 to 75 seconds or approximately 1.5 to 2.0 times the control value.<sup>494</sup> Because of the clear evidence that the measured effect of heparin on the aPTT is important for patient outcome and that the predominant variable mediating the effect of a given dose of heparin is weight,<sup>494</sup> it is important to administer the initial doses of heparin as a weight-adjusted bolus.<sup>481</sup> A 70 U/kg bolus followed by 15 U/kg per hour has been useful, although other mitigating factors including age and gender, require careful aPTT measurement and dose adjustment. More recent information for both heparin and the novel antithrombin agent hirudin indicate that when used with thrombolytic therapy, an aPTT goal of 60 to 90 seconds is associated with an unacceptably high rate of ICH.<sup>495,496</sup>

An algorithm for heparin dosing in the setting of thrombolytic therapy or treatment of non-ST-segment elevation is provided in Table 9. It is important to check the aPTT 4 to 6 hours after initiating therapy or changing dose, given the information about increased risk with a high aPTT. Considering the substantial delay in reporting aPTT values in many hospitals, the use of bedside coagulation monitoring,<sup>497</sup> if reliably performed, may be helpful.

The previous ACC/AHA guidelines on acute MI recommended low-dose subcutaneous heparin (5000 U every 12 hours for 24 to 48 hours) in all MI patients without contraindication who were not otherwise being treated with heparin for another reason. Current recommendations call for 7500 U twice a day (ACCP guidelines).<sup>423</sup> The empirical basis for this recommendation was the demonstration that deep venous thrombosis was reduced from 12% to 4% in an overview of three randomized controlled trials.<sup>498</sup> Continued adherence to this standard is reasonable, although routine earlier mobilization and use of aspirin may make this treatment unnecessary.

Once heparin has been started, the appropriate duration of therapy is uncertain. Based on the evidence for disruption of the atherosclerotic plaque and the concept that a healed endothelial surface would be salutary, a duration of 3 to 5 days has been standard. The only randomized trial to address this issue found, however, that discontinuation of heparin after 24 hours following thrombolytic therapy with alteplase resulted in no measurable increase in ischemic events,<sup>499</sup> although this study did not have adequate power to detect modest differ-

ences. A reasonable approach is to use intravenous heparin for 48 hours and then to use heparin according to the clinical characteristics of the patients. Heparin may be discontinued in low-risk patients, given subcutaneously in patients at high risk of systemic embolization, and intravenously in patients at high risk for coronary reocclusion.

Concern is mounting that when heparin is discontinued abruptly, the patient undergoes a high-risk period for recurrent thrombosis.<sup>500,501</sup> Despite this concern, no specific policy has been tested to attempt to reduce this clinical "rebound" effect. Several ongoing studies, however, are reducing heparin infusions in a gradual fashion (eg, by one half within 6 hours then discontinuing over the subsequent 12 hours).

Platelet counts should be monitored daily in patients on heparin. Recent evidence suggests the incidence of heparin-induced thrombocytopenia is 3% and is associated with a substantial risk of prothrombotic events.<sup>502</sup> If the platelet count drops below 100,000, a test for heparin-induced thrombocytopenia should be obtained, and the clinician should be vigilant for thrombotic complications as the prognosis in patients with thrombocytopenia is substantially worse.<sup>503</sup>

The deficiencies of heparin as an antithrombotic agent have been discussed in detail.<sup>504</sup> Fractionated heparins have been developed with variable effects on inhibition of thrombin and factor Xa. Although unfractionated heparin and low molecular weight heparin both catalyze the inhibition of thrombin by AT-III at clinically administered doses, the higher ratio of anti-Xa:anti-IIa activity of low molecular weight heparins offers the potential advantage of inhibiting the coagulation cascade at a more proximal step, leading to reduction in the generation of thrombin.<sup>505</sup> The addition of a low molecular weight heparin preparation to a regimen of aspirin,  $\beta$ -adrenoceptor blockers, and nitrates in patients with unstable angina/non-Q wave MI is superior to placebo for reducing the risk of death and nonfatal MI in hospital,<sup>506</sup> although this effect was lessened in longer-term follow-up. Some evidence exists that subcutaneous administration of a low molecular weight heparin appears to be superior to infusion of unfractionated heparin for reducing episodes of recurrent ischemia in patients with unstable angina.<sup>507</sup> These agents are superior in many forms of venous thrombosis,<sup>508</sup> but their relative value in coronary arterial thrombosis has not been established.

Newer direct antithrombin agents are also in an advanced stage of development. The prototypical direct antithrombin agent hirudin was initially isolated from the saliva of the medicinal leech. Now, synthesized by recombinant technology, this compound has several conceptual advantages: it does not require AT-III for its activity, it is not neutralized by plasma proteins, and it is able to inhibit clot-bound thrombin. Its characteristics also yield a stable aPTT value for a given dose, although its predominant renal excretion leads to unpredictable buildup in patients with significant renal dysfunction. After very promising early phase trials in acute MI<sup>509,510</sup> and unstable angina,<sup>511</sup> large-scale trials were initiated but had to be reconfigured due to an excess rate of ICH in patients treated with thrombolytic agents.<sup>495,496</sup> The GUSTO-IIb

study comparing hirudin with heparin in conjunction with standard medical therapy in the management of 12,142 patients with acute coronary syndromes recently reported a 30-day death or MI rate (primary end point) of 8.9% for patients randomly assigned to hirudin treatment versus 9.8% for those randomly assigned to heparin ( $P=.058$ ).<sup>512</sup> The TIMI 9B trial of 3002 patients receiving either TPA or streptokinase for ST-segment elevation MI reported a 30-day rate of death, MI, or severe CHF of 11.9% in patients randomly assigned to heparin compared with 12.9% in patients assigned to hirudin.<sup>512a</sup>

### Antiarrhythmics

Antiarrhythmic therapy plays an important but more limited role in acute MI care than in the past, as summarized in "Hospital Management." The use of anticholinergic therapy with atropine for bradyarrhythmias is summarized in "Hospital Management." This section briefly summarizes antiarrhythmic agents in Vaughan-Williams Classes I through III that are appropriate in the acute setting and can be intravenously administered. Use of agents from Classes II ( $\beta$ -adrenoceptor blockers) and IV (calcium-channel entry blockers) have several other mechanisms of action (anti-ischemic, antihypertensive, etc), and their use is primarily summarized in subsequent sections. In general, both acute and long-term antiarrhythmic therapy except with  $\beta$ -adrenoceptor blocking agents is indicated only for life-threatening or severely symptomatic arrhythmias and not for risk reduction in patients with non-life-threatening arrhythmias.

### Lidocaine

Lidocaine is a local anesthetic with antiarrhythmic properties, grouped in Class Ib based on its relatively rapid onset and offset kinetics of membrane sodium channel blockade. Lidocaine is metabolized in the liver; its volume of distribution and rate of clearance are reduced in heart failure.<sup>513</sup> Previous randomized studies have shown that it reduces risk for primary VF in both prehospital and early hospital settings.<sup>514,515</sup> Despite this fact, mortality is not reduced; indeed, VF deaths are offset by deaths associated with asystole and electromechanical dissociation.<sup>515,516</sup>

Lidocaine is the drug of choice in the setting of acute MI when treatment is indicated for premature ventricular complexes, VT, or VF. It is generally well tolerated, except in patients with shock. In the most recent adult ACLS protocol,<sup>517</sup> lidocaine is recommended as the first antiarrhythmic agent to be used in cardiac arrest patients with persistent VT/VF despite defibrillation and epinephrine, to prevent recurrence, to control unsustained ventricular ectopy requiring therapy, and to treat wide complex tachycardia of uncertain type.<sup>518,519</sup>

Lidocaine is given in an initial bolus of 1.0 to 1.5 mg/kg (75 to 100 mg); additional boluses of 0.5 to 0.75 mg/kg (25 to 50 mg) can be given every 5 to 10 minutes if needed up to a total of 3 mg/kg. This is followed by a maintenance infusion of

1 to 4 mg/min, reduced after 24 hours (to 1 to 2 mg/min) or in the setting of altered metabolism (heart failure, hepatic congestion, etc) and as guided by blood level monitoring.

### Bretlyium

Bretlyium is a quaternary ammonium compound with both direct (Class III) and indirect (sympathetic neuronal) actions. Its hemodynamic and electrophysiological profile are biphasic, with initial norepinephrine release from adrenergic nerve endings causing hypertension, tachycardia, shortening of AV nodal refractory periods, and subsequent neuronal blockade leading to hypotension<sup>520</sup>; clinical Class III effect (refractory period lengthening) also emerges with some (variable) delay. Experimentally and clinically, bretlyium has potent antifibrillatory but weak antiarrhythmic effects.

Clinically bretlyium is used in treatment of resistant VF and hemodynamically unstable VT. It is not a first-line agent but is recommended in the current ACLS protocol after defibrillation, epinephrine, and lidocaine have failed to convert VF (or pulseless VT) or after VF has recurred despite epinephrine and lidocaine. It may be used for VT in patients with a pulse, but only after lidocaine and procainamide have failed.

For VF, bretlyium is given as a 5 mg/kg bolus; if VF-related cardiac arrest persists, supplemental doses of 10 mg/kg can be given at 5-minute intervals to a maximum dose of 30 to 35 mg/kg. In stable VT the loading dose is diluted to 50 mL with 5% dextrose and given over 8 to 10 minutes. Bretlyium therapy is maintained with an infusion rate of 1 to 2 mg/min.

### Procainamide

Procainamide is an antiarrhythmic drug grouped in Class Ia because of its intermediate onset and offset kinetics of membrane sodium channel blockade. Procainamide has local anesthetic properties and mild to moderate hypotensive and negative inotropic potential. Its rate of metabolism to N-acetyl-procainamide (NAPA), which has Class III antiarrhythmic activity, is bimodally distributed in the population (fast, slow acetylators).

Procainamide is indicated for life-threatening ventricular arrhythmias but usually not as the drug of first choice. Procainamide suppresses premature ventricular complexes and recurrent VT and may be used when therapy is required when lidocaine has failed or is contraindicated. It may also be used for wide complex tachycardias of uncertain mechanism, although it also is usually not the drug of first choice in this setting. ACLS guidelines list procainamide as potential therapy for VF and pulseless VT refractory to defibrillation and epinephrine after lidocaine, bretlyium, and magnesium have been considered.<sup>517</sup>

Intravenous procainamide is initiated with a loading infusion of 10 to 15 mg/kg (500 to 1250 mg), given at a rate of 20 mg/min (ie, over 30 to 60 minutes), followed by a maintenance infusion of 1 to 4 mg/min. In responding patients, therapy may be continued orally as needed.

Procainamide may cause proarrhythmia, including torsades de pointes. Patients with renal insufficiency may develop high

levels of NAPA and are at increased risk for development of torsades.

### $\beta$ -Adrenoceptor Blockers

$\beta$ -Adrenoceptor blockers such as propranolol, metoprolol, and atenolol have been shown to reduce incidence of VF in patients with acute MI in studies preceding the reperfusion era.<sup>521</sup>  $\beta$ -Adrenoceptor blockers also may be of particular value early in the management of "electrical storm" (recurrent, polymorphic VT/VF) in the setting of recent MI, which is often unresponsive to standard antiarrhythmic therapy.<sup>521</sup> Additional rationale for  $\beta$ -adrenoceptor blocker use in acute MI is provided in the following section.

### Amiodarone

Amiodarone is a complex antiarrhythmic with action in each of the four Vaughn-Williams classes. Its mechanisms of action when given over the short term are still poorly defined but may include (1) noncompetitive  $\beta$ -adrenoceptor blockade, (2) calcium channel blockade, (3) blockade of sympathetic efferents, and (4) possible Class Ia effects.<sup>522</sup> Short-term (intravenous) amiodarone, unlike long-term (oral) administration may have little Class III effect. Intravenous amiodarone is now approved for treatment and prophylaxis of frequently recurring VF and hemodynamically destabilizing VT. If successful, therapy can be continued orally over the long term. In randomized studies in VF or destabilizing VT refractory to lidocaine, a dose response was observed between larger (500 to 1000 mg/d) and small (125 mg/d) doses of amiodarone in time to first VT/VF recurrence, although not in mortality.<sup>522</sup> Amiodarone also was equally as effective as bretlyium in preventing VT/VF recurrence but was better tolerated (less hypotension).<sup>523</sup>

Because of individual variability, dosing of intravenous amiodarone should be titrated according to patient response. The recommended starting dose is 500 mg per 24 hours, given in three stages: (1) rapid infusion of 150 mg over 10 minutes, (2) an early maintenance infusion of 1 mg/min for 6 hours, and (3) later maintenance infusion of 0.50 mg/min. Intravenous amiodarone is reasonably well tolerated, but adverse effects such as hypotension, bradycardia, and AV block may occur. With greater experience, amiodarone may become a preferred antiarrhythmic agent for intravenous therapy of life-threatening ventricular tachyarrhythmias in lidocaine failures.

### $\beta$ -Adrenoceptor Blocking Agents

#### Recommendations for Early Therapy (see also "Predischarge Preparation")

##### Class I

1. Patients without a contraindication to  $\beta$ -adrenoceptor blocker therapy who can be treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy.

2. Patients with continuing or recurrent ischemic pain.

**3. Patients with tachyarrhythmias, such as AF with a rapid ventricular response.**

**Class IIb**

**1. Non-Q wave MI.**

**Class III**

**1. Patients with moderate or severe LV failure or other contraindications to  $\beta$ -adrenoceptor blocker therapy.**

$\beta$ -Adrenoceptor blocking agents may be given to patients with acute MI to reduce morbidity and/or mortality during (1) the initial hours of evolving infarction and (2) the weeks, months, and years after completed infarction (secondary prevention).

During the first few hours of infarction,  $\beta$ -adrenoceptor blocking agents may diminish myocardial oxygen demand by reducing heart rate, systemic arterial pressure, and myocardial contractility. In addition, prolongation of diastole caused by a reduction in heart rate may augment perfusion to injured myocardium, particularly the subendocardium. As a result, immediate  $\beta$ -adrenoceptor blocker therapy appears to reduce (1) the magnitude of infarction and incidence of associated complications in subjects not receiving concomitant thrombolytic therapy and (2) the rate of reinfarction in patients receiving thrombolytic therapy.

In subjects not receiving thrombolytic therapy, intravenously administered  $\beta$ -adrenoceptor blocking agents exert a modestly favorable influence on infarct size<sup>524</sup>). More important, they diminish short-term mortality. In the First International Study of Infarct Survival,<sup>525</sup> in which more than 16 000 patients with suspected acute MI were enrolled within 12 hours of onset of symptoms, immediate intravenous atenolol, 5 to 10 mg, followed by oral atenolol, 100 mg daily, reduced 7-day mortality from 4.3% to 3.7% ( $P<.02$ ; 6 lives saved per 1000 treated). The mortality difference between those receiving and not receiving atenolol was evident by the end of day 1 and was sustained subsequently. In the Metoprolol in Acute Myocardial Infarction (MIAMI) trial<sup>526</sup> more than 5700 subjects with evolving MI were randomly assigned to receive placebo or metoprolol, up to 15 mg intravenously in 3 divided doses followed by 50 mg orally every 6 hours for 48 hours and then 100 mg twice a day thereafter. Fifteen-day mortality was reduced with metoprolol from 4.9% to 4.3%. As in ISIS-1, the mortality difference between those given placebo and those receiving metoprolol was evident by the end of day 1, after which it was sustained.

In subjects receiving concomitant thrombolytic therapy, intravenously administered  $\beta$ -adrenoceptor blocking drugs diminish the incidence of subsequent nonfatal reinfarction and recurrent ischemia; in addition, they may reduce mortality if given particularly early (ie, within 2 hours) after onset of symptoms. In the TIMI-II trial,<sup>107</sup> in which all patients received intravenous alteplase, those randomly assigned to receive intravenous metoprolol, 15 mg, followed by oral metoprolol, 50 mg twice a day for 1 day and then 100 mg twice a day thereafter, had a diminished incidence of subsequent nonfatal

reinfarction and recurrent ischemia when compared with those begun on oral metoprolol 6 days after the acute event. Among those treated especially early, ie, within 2 hours of symptom onset, the composite end point, death or reinfarction, occurred less often in those given immediate intravenous metoprolol than in those who did not receive it.

If intravenous  $\beta$ -adrenoceptor blockade induces an untoward effect, such as AV block, excessive bradycardia, or hypotension, the condition is quickly reversed by infusion of a  $\beta$ -adrenergic agonist (ie, isoproterenol, 1 to 5  $\mu$ g/min).

**Contraindications**

The following are relative contraindications to  $\beta$ -adrenoceptor blocker therapy:

- Heart rate less than 60 bpm
- Systolic arterial pressure less than 100 mm Hg
- Moderate or severe LV failure
- Signs of peripheral hypoperfusion
- PR interval greater than 0.24 second
- Second- or third-degree AV block
- Severe chronic obstructive pulmonary disease
- History of asthma
- Severe peripheral vascular disease
- Insulin-dependent diabetes mellitus

*Angiotensin Converting Enzyme Inhibitors*

**Recommendations**

**Class I**

**1. Patients within the first 24 hours of a suspected acute MI with ST-segment elevation in two or more anterior precordial leads or with clinical heart failure in the absence of significant hypotension or known contraindications to use of ACE inhibitors.**

**2. Patients with MI and LV ejection fraction less than 40% or patients with clinical heart failure on the basis of systolic pump dysfunction during and after convalescence from acute MI.**

**Class IIa**

**1. All other patients within the first 24 hours of a suspected or established acute MI, provided significant hypotension or other clear-cut contraindications are absent.**

**2. Asymptomatic patients with mildly impaired LV function (ejection fraction 40% to 50%) and a history of old MI.**

**Class IIb**

**1. Patients who have recently recovered from MI but have normal or mildly abnormal global LV function.**

A number of large, randomized clinical trials have assessed the role of ACE inhibitors early in the course of acute MI. All trials in which only oral ACE inhibitors were used demonstrated a benefit in mortality. The only trial not showing benefit using ACE inhibitors was the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II, in which patients were randomly assigned within the first day to receive either

intravenous enalaprilat or placebo followed by increasing oral dosages of either enalapril or placebo. This trial was terminated early by the Safety Committee because of the high probability that a significant beneficial effect of enalapril over placebo was unlikely to be demonstrated with continuation of the trial, as well as a concern over an adverse effect among elderly patients experiencing an early hypotensive reaction.<sup>527</sup> The 95% confidence limits ranged from showing a 7% benefit to 29% harm.

Clarification of the role of ACE inhibitors early in the course of MI has more recently resulted from large-scale clinical trials in which oral ACE inhibitors were used. In the ISIS-4 trial 58 000 patients with suspected acute MI were randomly assigned within the first 24 hours (median 8 hours) to receive either oral captopril or placebo; a significant 7% proportional reduction was observed in 5-week mortality among those randomly assigned to captopril.<sup>421</sup> The largest benefit was among those with an anterior infarction.<sup>528</sup> Among the 143 fewer deaths in the group allocated captopril, 44 occurred in days 0 through 1 and 37 in days 2 through 7,<sup>529</sup> demonstrating that early therapy is important. The GISSI-3 trial used oral lisinopril in over 19 000 patients with either ST-segment elevation or depression who were randomly assigned to it or open control.<sup>420</sup> There was a significant reduction in 6-week mortality (odds ratio 0.88; 95% CI, 0.79 to 0.99); 60% of the lives were saved during the first 5 days of treatment. The SMILE (Survival of Myocardial Infarction: Long-Term Evaluation) study involved 1556 patients randomly assigned within 24 hours to receive either placebo or zofenopril.<sup>530</sup> The patient population was restricted to those with anterior MI who had not received thrombolytic therapy. Use of an early ACE inhibitor in this trial suggested a strong trend of more lives saved in the first 6 weeks (RR 25%, P=.19). A Chinese captopril pilot study involving more than 13 600 patients with suspected acute MI also revealed an approximate 0.5% absolute mortality benefit among those who were randomly assigned to the ACE inhibitor compared with the control population.<sup>531</sup> A meta-analysis of these major trials along with 11 smaller trials that involve more than 100 000 patients reveals a 6.5% overall odds reduction ( $2P=.006$ ) with an absolute benefit of 4.6 fewer deaths per 1000 patients treated among those who received the ACE inhibitor.<sup>529</sup> These data suggest that ACE inhibitors have a role in early management as well as in the convalescent phase of acute MI.

Although detailed subgroup analysis of the ISIS-4 and GISSI-3 trials awaits further publication, it would appear that the benefits of ACE inhibitors are greater among those with an anterior infarct or who have evidence of previous infarction, heart failure, and tachycardia, ie, those at highest risk. Nevertheless, all trials with oral ACE inhibitors have shown benefit from its early use, including those in which entry criteria included all suspected acute infarctions. Data from these trials indicate that ACE inhibitors should generally be started within the first 24 hours, ideally, after thrombolytic therapy has been completed and blood pressure has sta-

bilized. When there are no patient complications and no evidence of symptomatic or asymptomatic LV dysfunction by 4 to 6 weeks, ACE inhibitors can be stopped. ACE inhibitors should not be used if systolic blood pressure is less than 100 mm Hg, if clinically relevant renal failure is present, if there is a history of bilateral stenosis of the renal arteries, or if there is known allergy to ACE inhibitors. ACE inhibitor therapy should start with low-dose oral administration and increase steadily to achieve a full dose within 24 to 48 hours. For example, in ISIS-4 an initial 6.25 mg dose of captopril was given, followed by 12.5 mg 2 hours later, 25 mg 10 to 12 hours later, and then 50 mg twice a day. GISSI patients received 5 mg oral lisinopril at the time of randomization, 5 mg after 24 hours, 10 mg after 48 hours, then 10 mg daily for 6 weeks or open control. Similar graded-dose schedules should be used with other ACE inhibitors, such as ramipril, zofenopril, enalapril, or quinapril. Intravenous enalaprilat should be avoided.

### *Calcium Channel Blockers*

#### **Recommendations**

##### **Class I**

None.

##### **Class IIa**

1. Verapamil or diltiazem may be given to patients in whom  $\beta$ -adrenoceptor blockers are ineffective or contraindicated (ie, bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with AF after acute MI in the absence of CHF, LV dysfunction, or AV block.

##### **Class IIb**

1. In non-ST-elevation infarction, diltiazem may be given to patients without LV dysfunction, pulmonary congestion, or CHF. It may be added to standard therapy after the first 24 hours and continued for 1 year.

##### **Class III**

1. Nifedipine (short acting) is generally contraindicated in routine treatment of acute MI because of its negative inotropic effects and the reflex sympathetic activation, tachycardia, and hypotension associated with its use.

2. Diltiazem and verapamil are contraindicated in patients with acute MI and associated LV dysfunction or CHF.

**Comment:** Calcium channel blocking agents have not been shown to reduce mortality after acute MI, and in certain patients with cardiovascular disease there are data to suggest they are harmful.<sup>532</sup> It is the consensus of this committee that these agents are still used too frequently<sup>84</sup> in patients with acute MI and that  $\beta$ -adrenoceptor blocking agents are a more appropriate choice across a broad spectrum of patients with acute MI (with exceptions as noted).

#### **Nifedipine**

In patients with acute MI, immediate-release nifedipine does not reduce incidence of reinfarction or mortality when

given early (less than 24 hours) or late after acute MI. This lack of benefit is found in all patients, irrespective of gender, overall risk, type of infarction (Q wave versus non-Q wave), and presence or absence of concomitant  $\beta$ -adrenoceptor blocking agents or thrombolytic therapy. Immediate-release nifedipine may be particularly detrimental in patients with hypotension and/or tachycardia; in these patients it may induce a reduction in coronary perfusion pressure, disproportionate dilatation of the coronary arteries adjacent to the ischemic area (so-called "steal"), and/or reflex activation of the sympathetic nervous system, with an increase in myocardial oxygen demands. These findings are based on numerous clinical trials, including the Nifedipine Angina Myocardial Infarction Study (NAMIS),<sup>533</sup> the Norwegian Nifedipine Multicenter Trial,<sup>534</sup> the Trial of Early Nifedipine Treatment in Acute Myocardial Infarction (TRENT),<sup>535</sup> and the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT).<sup>536,537</sup> These studies were performed using first-generation nonsustained-release nifedipine. Whether the conclusions are valid for the entire class of agents is unknown.<sup>531,532,538</sup>

### Verapamil

Although the overall results of trials with verapamil showed no mortality benefits, subgroup analysis showed that immediate-release verapamil initiated several days after acute MI in patients who were not candidates for a  $\beta$ -adrenoceptor blocking agent may be useful in reducing the incidence of the composite end point of reinfarction and death, provided LV function is well preserved with no clinical evidence of heart failure. Verapamil is detrimental to patients with heart failure or bradyarrhythmias during the first 24 to 48 hours after acute MI.<sup>539,542</sup> One randomized study of 1700 patients, less than 75 years of age, using verapamil within 2 weeks of acute MI showed a 16.7% reduction in major events (death or MI) over 18 months.<sup>543</sup>

### Diltiazem

Data from the Multicenter Diltiazem Postinfarction Trial (MDPIT) (Q wave and non-Q wave infarction)<sup>544</sup> and the Diltiazem Reinfarction Study (DRS) (non-Q wave infarction)<sup>540,541,545,546</sup> suggest that patients with non-Q wave MI or those with Q wave infarction, preserved LV function, and no evidence of heart failure may benefit from immediate-release diltiazem. Diltiazem was begun in MDPIT 3 to 15 days after acute MI and in DRS 24 to 72 hours afterward. The results of MDPIT may be confounded by the fact that 53% and 55% of placebo- and diltiazem-treated patients, respectively, received concomitant  $\beta$ -adrenoceptor blocker therapy.<sup>544</sup> Also, both the MDPIT and DRS projects were conducted in an era when the use of aspirin was not as prevalent as it is today, raising further uncertainty about the relevance of their findings for contemporary management of acute MI. Of particular clinical importance is the detrimental mortality effect of diltiazem in patients with LV dysfunction.

The INTERCEPT trial (Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post Throm-

bolysis) (diltiazem) will test the hypothesis that use of sustained-release diltiazem in patients receiving thrombolytic therapy for a first MI will decrease mortality, reinfarction, and angina.<sup>547</sup>

### Summary of Calcium Channel Blockers

Calcium channel blockers have not proven beneficial in early treatment or secondary prevention of acute MI, and the possibility of harm has been raised. In patients with first non-Q wave infarction or first inferior infarction without LV dysfunction or pulmonary congestion, verapamil and diltiazem may reduce the incidence of reinfarction, but their benefit beyond that of  $\beta$ -adrenoceptor blockers and aspirin is unclear. Similarly, there are no data to support the use of second-generation dihydropyridines (eg, amlodipine, felodipine) for improving survival in acute MI.

### Magnesium

#### Recommendations

##### Class I

None.

##### Class IIa

**1. Correction of documented magnesium (and/or potassium) deficits, especially in patients receiving diuretics before onset of infarction.**

**2. Episodes of torsades de pointes-type VT associated with a prolonged QT interval should be treated with 1 to 2 g magnesium administered as a bolus over 5 minutes.**

##### Class IIb

**1. Magnesium bolus and infusion in high-risk patients such as the elderly and/or those for whom reperfusion therapy is not suitable.**

*Comment:* The available data suggest that mortality reduction may be seen in high-risk patients, provided magnesium therapy is administered soon after onset of symptoms (preferably less than 6 hours). The optimum dose has not been established, but a bolus of 2 g over 5 to 15 minutes followed by an infusion of 18 g over 24 hours has been used with success.

### Background

Supplemental administration of magnesium for reducing morbidity and mortality in patients with acute MI is a reasonable avenue to pursue because of abundant data relating magnesium to cardiovascular disease.<sup>548</sup> It is the second most abundant intracellular cation and is involved in more than 300 enzymatic processes. Evidence exists that magnesium produces systemic and coronary vasodilatation, possesses antiplatelet activity, suppresses automaticity in partially depolarized cells, and protects myocytes against calcium overload under conditions of ischemia by inhibiting calcium influx especially at the time of reperfusion.<sup>548-552</sup>

Meta-analyses of the seven randomized trials published between 1984 and 1991 suggest a significant mortality benefit of magnesium (odds ratio 0.44, CI 0.27 to 0.71).<sup>553,554</sup> The

**Table 10.** A Classification of Inotropic Agents

Agent	Mechanism	Inotropic	Vascular Effect	Major Use
Isoproterenol	$\beta$ -1 receptor	++	Dilatation	Hypotension due to bradycardia; no pacing available
Dobutamine	$\beta$ -1 receptor	++	Mild dilatation	Low output with SBP >90 mm Hg
Dopamine	Low dose: dopaminergic receptor  Medium dose: $\beta$ -1 receptor  High dose: $\alpha$ receptor  $\alpha$ Receptor	++	Renovascular dilation  Constriction  Intense constriction  Intense constriction	Hypoperfusion with SBP <90 mm Hg or $\geq$ 30 mm Hg below usual value
Norepinephrine		++		Extreme hypotension despite use of dopamine
Amrinone	Phosphodiesterase inhibitor	++	Dilatation	Second-tier agent after failure of dopamine/dobutamine
Milrinone	Phosphodiesterase inhibitor	++	Dilatation	
Digitalis	Inhibits NA <sup>+</sup> -K <sup>+</sup> ATPase pump	+	Variable	Established systolic LV dysfunction and symptoms of heart failure for chronic therapy

SBP indicates systolic blood pressure; LV, left ventricular.

Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) trial<sup>555</sup> subsequently reported a 24% reduction in mortality with magnesium treatment ( $P<.04$ ). The magnesium-treated patients in LIMIT-2 had a 25% lower incidence of CHF in the CCU and a 21% lower rate of ischemic heart disease-related mortality over 4 years, consistent with the hypothesis that magnesium exerts its beneficial effects, at least in part, via a myocardial protective action.<sup>555,556</sup>

The results of one large trial were negative. The ISIS-4 investigators enrolled 58 050 patients, 29 011 allocated to magnesium, and 29 039 to control. There were 2216 deaths (7.64%) by 35 days in the magnesium group and 2103 deaths (7.24%) in the control group (odds ratio 1.06; CI 0.99 to 1.13), suggesting no mortality benefit of magnesium administration and even the possibility of slight harm.<sup>421</sup> When ISIS-4 is added to the preceding randomized trials, meta-analysis indicates no beneficial effect of magnesium. Possible sources of heterogeneity that could explain these differences include:

1. The relatively late administration of magnesium in ISIS-4.<sup>557</sup>
2. The control group mortality in ISIS-4 was only 7.2%. Regression analyses of the available data predict a null effect of magnesium when the control mortality is about 7% and increasing benefit of magnesium for higher control mortality rates.<sup>558</sup>

Shechter and colleagues<sup>559</sup> recently reported a randomized trial of 194 patients with acute MI unsuitable for thrombolysis. There was a significant reduction in mortality in the magnesium group (4.2% versus 17.3%,  $P<.01$ ), largely due to a lower incidence of cardiogenic shock and CHF.

An NHLBI-sponsored trial (Magnesium in Coronary Disease [MAGIC]) is planned to further evaluate the role of magnesium in acute MI, especially with early administration before thrombolysis in higher-risk patients.<sup>557</sup>

### Inotropic Agents

It is useful clinically to consider inotropic agents in terms of three classes (Table 10): inotropic agents with predominant vasoconstrictive properties; catecholamines with predominant inotropic properties with little or no vasoconstriction; and phosphodiesterase inhibitors, inotropic agents with predominant vasodilating properties.

Vasoconstrictor inotropic agents are represented by dopamine and norepinephrine. Contractility and heart rate are increased by dopamine through its direct stimulation of  $\alpha$  and  $\beta$ -adrenergic receptors and through release of norepinephrine from nerve endings. When given in low doses (1 to 3  $\mu$ g/kg per minute), its major effects are on dopaminergic receptors leading to renovascular dilatation and on  $\beta$  adrenoceptors modestly stimulating contractility. At a dose of 5 to 10  $\mu$ g/kg per minute, the  $\beta$ -1 receptor effects are dominant, leading to an increase in contractility and heart rate. At higher doses the  $\alpha$ -receptor effects predominate, leading to vasoconstriction. Norepinephrine is almost purely a vasoconstrictive agent with a positive effect on contractility.

The catecholamine inotropic agents that do not cause vasoconstriction are represented by dobutamine. Through its effects on  $\beta$ -1 receptors, it stimulates contractility; the hope that it would produce less tachycardia and fewer arrhythmias than dopamine has not been realized. Isoproterenol produces increased heart rate and contractility while causing vasodilation; therefore, it is not recommended except as an emergency measure when low output is caused by a profound bradycardia and temporary pacing is not available.

Amrinone and milrinone (phosphodiesterase inhibitors) were developed with the hope that their different mechanism of action would lead to improved cardiac output without the risk of arrhythmia engendered by catecholamines. These agents are characterized by both inotropic and vasodilating effects and with a more substantial effect on preload than

catecholamines. Excessive mortality when oral milrinone was given long term and unacceptable toxicity of long-term use of amrinone<sup>560</sup> have dampened enthusiasm for long-term use of these drugs. Renal elimination of phosphodiesterase inhibitors is a problem in critically ill patients.

In a patient with perceived low output, the clinician must simultaneously assess the patient for the possible cause and institute life-saving therapy. If volume depletion is a possible cause, an intravascular volume-expanding infusion should be initiated. When blood pressure is low (systolic less than 90 mm Hg or 30 points below usual), dopamine is the agent of first choice. If blood pressure remains low with institution of more than 20 µg/kg, norepinephrine may be substituted in doses of 2 to 20 µg/kg per minute. In all other situations dobutamine is the agent of first choice. All intravenous catecholamines have the advantage of a very short half-life, enabling titration of the dose in a matter of minutes while observing the clinical effect.

Phosphodiesterase inhibitors are reserved for patients who have not responded to catecholamines or who have significant arrhythmias or ischemia-producing tachycardia on catecholamine therapy. Milrinone is given in a dose of 0.25 to 0.75 µg/kg per minute. Special caution must be advised in patients with renal dysfunction because the drug will accumulate.

In general the current concept is that patients requiring intravenous inotropic support should be maintained on these agents for as short a time as possible. These agents are arrhythmogenic and increase myocardial oxygen demand. The only available empirical information on mortality effects with long-term use are dismal. Whenever possible, afterload reducing agents and intra-aortic balloon pumping should be substituted for inotropic agents.

### Digitalis

Despite the initial description of the inotropic properties of digitalis in 1785, its role in the post-MI patient remains controversial. Concern about increased mortality associated with long-term use of milrinone has fueled a reexamination of the empirical information about digitalis from previous observational studies. These studies had mixed results, with some suggesting an increase in mortality and others a neutral effect on mortality.<sup>561</sup> Recent studies have demonstrated that in patients with definite systolic LV dysfunction, digitalis improves symptomatic status and has a favorable effect on the neurohormonal system.<sup>562,563</sup> The Digitalis Investigator Group (DIG) recently reported a study of 7788 patients in CHF (due to ischemic heart disease in 70% of cases) who were in sinus rhythm. Digoxin was compared with placebo for prevention of all-cause mortality.<sup>564</sup> More than 90% of patients were also on ACE inhibitors and/or diuretics. Important secondary objectives included hospitalization for CHF, cardiovascular mortality, and death due to CHF. The overall findings of the trial showed no reduction in total mortality with digoxin. However, there were reductions in deaths due to CHF and combined heart failure-related deaths and hospitalizations in digoxin-

treated patients. A trend toward increased deaths due to presumed arrhythmia or MI was observed in the digoxin group. Of note, a recent MI was an exclusion criterion for enrollment in the DIG trial. Thus, the current recommendation, based on previous clinical experience, supports the use of digoxin in selected patients recovering from an MI if they have supraventricular arrhythmias or CHF refractory to ACE inhibitors or diuretics. Generally the loading dose is 8 to 15 µg/kg lean body weight, with half the dose given immediately and the remainder given in 25% increments 6 hours apart. A maintenance dose of 0.125 to 0.375 mg/d is given, based on renal function and lean body weight.

## VI. Preparation for Discharge From the Hospital

### *Noninvasive Evaluation of Low-Risk Patients*

#### Recommendations

##### *Class I*

###### 1. Stress ECG

a. Before discharge for prognostic assessment or functional capacity (submaximal at 4 to 6 days or symptom limited at 10 to 14 days).

b. Early after discharge for prognostic assessment and functional capacity (14 to 21 days).

c. Late after discharge (3 to 6 weeks) for functional capacity and prognosis if early stress was submaximal.

2. Exercise, vasodilator stress nuclear scintigraphy, or exercise stress echocardiography when baseline abnormalities of the ECG compromise interpretation.\*

##### *Class IIa*

1. Dipyridamole or adenosine stress perfusion nuclear scintigraphy or dobutamine echocardiography before discharge for prognostic assessment in patients judged to be unable to exercise.

2. Exercise two-dimensional echocardiography or nuclear scintigraphy (before or early after discharge for prognostic assessment).

##### *Class III*

1. Stress testing within 2 to 3 days of acute MI.

2. Either exercise or pharmacological stress testing at any time to evaluate patients with unstable postinfarction angina pectoris.

3. At any time to evaluate patients with acute MI who have uncompensated CHF, cardiac arrhythmia, or noncardiac conditions that severely limit their ability to exercise.

\*Marked abnormalities in the resting ECG such as LBBB, LV hypertrophy with strain, ventricular pre-excitation, or a ventricular paced rhythm render a displacement of the ST segments virtually uninterpretable. For patients taking digoxin or who have less than 1 mm ST depression on their resting tracing who undergo standard stress electrocardiographic testing, it must be realized that further ST depression with exercise may have minimal diagnostic significance.

**4. Before discharge to evaluate patients who have already been selected for cardiac catheterization.** In this situation an exercise test may be useful after catheterization to evaluate function or identify ischemia in distribution of a coronary lesion of borderline severity.

### Role of Exercise Testing

The role of exercise testing in evaluating patients after MI has been well established<sup>565</sup> and extensively covered in the earlier ACC/AHA guidelines.<sup>1,566,567</sup> The basic aims of early exercise testing after MI are to (1) assess functional capacity and the patient's ability to perform tasks at home and at work; (2) evaluate the efficacy of the patient's current medical regimen; and (3) risk-stratify the post-MI patient according to the likelihood of a subsequent cardiac event. Numerous studies reported throughout the 1980s provided particularly important information about risk stratification and the development of practical algorithms for further management of the post-MI patient.<sup>568-572</sup> The decade of the 1980s also witnessed a dramatic change in treatment of patients with acute MI, characterized most notably by the broad use of thrombolytic therapy beginning in 1988. Equally important has been the widespread use of aspirin,  $\beta$ -adrenoceptor blocking agents, vasodilator therapy, common use of ACE inhibitors, and a far more aggressive use of revascularization therapy in patients who have clinical markers of a poor prognosis. It is this constellation of new therapy and not solely the administration of thrombolytic therapy that marks what is generally referred to as the "reperfusion era."

This period has witnessed an impressive reduction in early and 1-year mortality rates for acute MI patients, which is particularly striking in patients who have received thrombolytic therapy and revascularization during hospitalization.<sup>573</sup>

The improvement in 1-year mortality in patients who have received thrombolytic therapy is multifactorial. Such patients are less likely to have severe three-vessel coronary artery disease.<sup>574</sup> Patients who receive thrombolytic therapy have a smaller infarct size.<sup>575</sup> Coronary angiography is frequently performed during hospitalization due to recurrent chest pain, which identifies many patients with severe disease who subsequently undergo revascularization.<sup>576</sup> The patient population eligible for predischarge exercise testing in clinical trials of thrombolytic therapy is therefore far different from less selected, historical populations. Their low cardiac event rate following discharge is therefore not surprising and substantially reduces the predictive accuracy of early exercise testing.

The highest-risk subset of patients are those who are unable to exercise.<sup>577,578</sup> Although patients with exercise-induced ST depression have a higher 1-year mortality than patients without exercise-induced depression, their absolute mortality remains low (1.7%) by historical standards.<sup>578</sup> The duration of exercise is also known to be an important predictor of outcomes and the ability to perform at least 5 metabolic equivalents (METs) without early exercise ST depression and show a normal rise in systolic blood pressure is important in constituting a negative predictive value.<sup>579,580</sup>

There is limited evidence on the ability of exercise testing to risk-stratify patients who have not received reperfusion in the current era. Although their subsequent mortality rates are lower because of the constellation of new therapy mentioned earlier, their absolute event rates are higher than in patients who have received thrombolytic therapy, particularly if they have also not undergone revascularization.<sup>573</sup> Although the available evidence is limited, exercise testing presumably can still assist in the risk stratification of such patients.

Low-level exercise testing appears to be safe if patients have undergone in-hospital cardiac rehabilitation, including low-level exercise, have had no symptoms of angina or heart failure, and have a stable baseline ECG 48 to 72 hours before the exercise test. Two different protocols have been used to determine the end points of these very early exercise tests.<sup>581-583</sup>

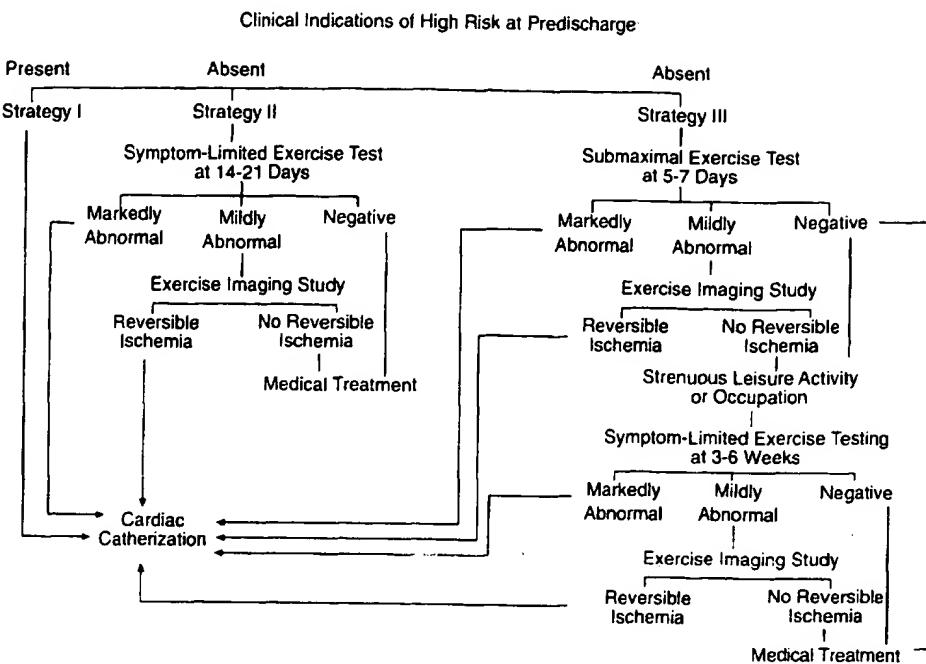
The traditional submaximal exercise test (done at 3 to 5 days in patients without complications) incorporates a series of end points, including a peak heart rate of 120 to 130 bpm or 70% of maximal predicted heart rate for age, a peak work level of 5 METs, or clinical or ECG end points of mild angina or dyspnea, ST-segment depression greater than 2 mm, exertional hypotension, or three or more consecutive premature ventricular contractions, whichever end point is reached first. The second protocol is performance of a symptom-limited exercise test (done at 5 days or later) without stopping for target heart rates or MET levels. Although this level appears to be safe and will result in a higher frequency of abnormal exercise tests, the prognostic value of ST depression occurring at higher work levels in deconditioned patients is uncertain and may lead to unnecessary cardiac catheterization.

The optimum time for performing the exercise test after MI remains unresolved. It is argued that a predischarge exercise test provides psychological benefits to the patient and will permit detection of profound ischemia that could be associated with postdischarge cardiac events that might occur before a scheduled 3- to 6-week postdischarge symptom-limited stress test. On the other hand, deferring exercise testing until approximately 3 weeks after MI in clinically low-risk patients appears safe and reasonable and enables more optimal assessment of functional capacity. For patients without complications who have not undergone coronary arteriography before discharge, it is the consensus of this committee that patients who might be potential candidates for revascularization procedures should undergo exercise electrocardiography before or just after discharge.

### Supplemental Imaging

#### Exercise Myocardial Perfusion Imaging

In a number of reports from a decade ago, before the use of thrombolytic therapy, the prognostic value of exercise myocardial perfusion imaging was found to be superior to that of exercise electrocardiographic testing.<sup>584-587</sup> Pharmacological stress perfusion imaging<sup>588-590</sup> was also shown to have value for the prediction of postinfarction cardiac events. The key issues are whether these results apply to current patient populations



**Figure 10.** Strategies for exercise test evaluations soon after myocardial infarction (MI). If patients are at high risk for ischemic events, based on clinical criteria, they should undergo invasive evaluation to determine if they are candidates for coronary revascularization procedures (Strategy I). For patients initially deemed to be at low risk at time of discharge after MI, two strategies for performing exercise testing can be used. One is a symptom-limited test at 14 to 21 days (Strategy II). If the patient is on digoxin or if baseline electrocardiogram precludes accurate interpretation of ST-segment changes (eg, baseline left bundle branch block or left ventricular hypertrophy), then an initial exercise imaging study can be performed. Results of exercise testing should be stratified to determine need for additional invasive or exercise perfusion studies. A third strategy is to perform a submaximal exercise test at 5 to 7 days after MI or just before hospital discharge. The exercise test results could be stratified using the guidelines in Strategy I. If exercise test studies are negative, a second symptom-limited exercise test could be repeated at 3 to 6 weeks for patients undergoing vigorous activity during leisure or at work.

in the reperfusion era and whether myocardial perfusion imaging is worth the additional cost for risk stratification.<sup>591</sup> The same issues outlined previously with respect to exercise electrocardiographic testing also apply to this methodology.

In patients with ST elevation who have received thrombolytic therapy, several studies using myocardial perfusion imaging have found that it is less valuable than previously for risk stratification,<sup>592-594</sup> primarily because of the low late cardiac event rate.

In patients in the current era who have not received reperfusion therapy, particularly those who have not undergone revascularization, the same considerations regarding subsequent patient outcome that were outlined above for exercise electrocardiographic testing apply. There is evidence that myocardial perfusion imaging is useful for risk stratification in such patients, despite their better overall prognosis.<sup>595</sup>

It seems likely that the previously demonstrated superiority of stress myocardial perfusion imaging probably continues to apply to this population, although there is limited evidence on this point. It must be recognized that prospective studies are difficult to conduct because clinicians frequently intervene in patients with abnormal predischarge stress perfusion imaging studies.

Myocardial perfusion imaging with either thallium 201<sup>596</sup> or technetium 99m sestamibi<sup>597</sup> can assess infarct size. The measurement of infarct size by either one of these techniques is significantly associated with subsequent patient mortality after thrombolytic therapy.<sup>596,597</sup> Data are also emerging to suggest that vasodilator stress nuclear scintigraphy is safe and can be used for early (48 to 72 hours) risk stratification.

Recommended strategies for exercise test evaluations soon after MI are presented in Fig 10.

### Role of Echocardiography

The widespread availability, portability, and relative cost of echocardiography has resulted in its increased use as a practical and reliable means of assessing both global ventricular function and regional wall motion abnormalities. The uses of echocardiography in acute MI are discussed in detail in the ACC/AHA guidelines for clinical application of echocardiography.<sup>87a</sup>

### Risk Stratification After Myocardial Infarction

The incremental value of exercise echocardiography over regular exercise testing after MI has also not been established. The usefulness of exercise echocardiography as a means of assessing myocardial ischemia in patients with coronary artery disease has been well established, with overall sensitivity of 81% and specificity of 89%.<sup>598-613</sup> However, its value in predicting cardiac events after MI has not been fully determined. A negative test is, in general, associated with a low risk of cardiac events and death, but it may be higher than that

associated with a negative perfusion scan.<sup>604-608</sup> The usefulness of pharmacological stress testing with echocardiography or single-photon emission computed tomography (SPECT) imaging using agents such as dipyridamole or dobutamine in predicting cardiac events after acute MI is also a subject undergoing intense investigation. A positive dipyridamole echocardiogram after MI is associated with a higher late mortality rate, but a negative test does not preclude cardiac events in the 2-year follow-up period.<sup>609</sup> There are few data regarding the prognostic value of a positive or negative dobutamine stress echocardiogram, but its safety in general and in the 3 to 5 days after MI<sup>610</sup> is acceptably low. This agent, although widely used for pharmacological stress testing, has not been approved for this purpose by the FDA. Like scintigraphy, there is great variation among institutions in expertise and study quality, and it is this local expertise that should determine the choice of test procedures. Exercise echocardiography generally, however, is a less costly procedure than radionuclide perfusion scintigraphy.

### **Myocardial Viability**

A significant development since the previous set of recommendations is related to understanding and identifying myocardial viability. Up to one third of patients who have significant LV dysfunction may improve with revascularization.<sup>611</sup> This usually refers to myocardial hibernation,<sup>611</sup> in which chronic low flow state is associated with depressed myocardial function. Myocardial stunning<sup>612</sup> is more germane to the situation after MI, when depressed ventricular function is present despite adequate restoration of blood flow. Function will subsequently improve. The therapeutic importance of myocardial stunning is perhaps less than hibernation because identification of the former does not in general initiate a change in management of revascularization. However, identification of extensive reversible LV dysfunction is of prognostic importance and may help to optimize medical management after MI.<sup>610</sup>

Several noninvasive imaging modalities have been established as accurate predictors of myocardial viability. These include thallium imaging, positron emission tomography (PET), and dobutamine echocardiography. The choice of which technique to use should be dependent on center and regional expertise. Positron emission tomography scanning is most sensitive in detecting viable myocardium, but because of the limitations described above and the expense involved, it has little widespread applicability. Thallium imaging has been well established over time, while dobutamine echocardiography seems to have an acceptably high positive predictive accuracy. More important than technique, however, is the question of whether myocardial viability tests should be used in practice until large-scale outcome data can validate the usefulness.

### **Left Ventricular Function**

Assessment of LV function after acute MI has been demonstrated to be one of the most accurate predictors of future

cardiac events in the risk stratification of patients with acute MI in both the prereperfusion<sup>613</sup> and the reperfusion eras.<sup>614,615</sup> Multiple techniques for assessing LV function of patients after infarction have been shown to have important prognostic value and include such basic principles as clinical estimates based on patients' symptoms (eg, exertional dyspnea, functional status), physical findings (eg, rales, elevated jugular venous pressure, cardiomegaly, S<sub>3</sub> gallop), exercise duration (treadmill time) and measurement of ejection fraction by contrast ventriculography, radionuclide ventriculography, and two-dimensional echocardiography. Zaret and colleagues<sup>614</sup> found that an LV ejection fraction less than 0.30 as assessed by radionuclide ventriculography was still predictive of mortality in patients surviving infarction treated with thrombolytic therapy, despite the significantly reduced mortality of these patients compared with those in the prereperfusion era. White and colleagues<sup>616</sup> performed contrast left ventriculography in 605 patients 1 to 2 months after MI. They found postinfarction LV dilation, demonstrated by increased end-systolic volume greater than 130 mL, was an even better predictor of mortality after MI than an LV ejection fraction less than 40% or increased end-diastolic volume. In patients with normal ejection fractions, however, end-systolic volume did not provide any further stratification according to risk.

### **Radionuclide Testing for the Diagnosis of Acute Myocardial Infarction**

Guidelines for cardiac radionuclide imaging have been published recently<sup>567</sup> that indicate the clinical use of radionuclide imaging for diagnosis of acute MI should be restricted to special limited situations in which the triad of history, electrocardiographic changes, and laboratory measurements is unavailable or less reliable.

In patients who present late (more than 24 hours and less than 7 days) without diagnostic electrocardiographic changes and in patients early after coronary artery bypass surgery, myocardial infarct-avid scintigraphy using <sup>99m</sup>Tc pyrophosphate has moderate sensitivity and specificity for the diagnosis of acute MI.<sup>617,618</sup> More recently infarct-avid scintigraphy with antimyosin antibody has been described as an alternative to pyrophosphate scintigraphy<sup>619,620</sup> and has just received FDA approval for use in the United States.

In selected patients with RV infarction, radionuclide imaging may also have a role in diagnosis by demonstrating a reduced RV ejection fraction and RV asynergy.<sup>621</sup>

Localized perfusion defects occur in a high percentage of patients with acute LV infarction associated with coronary occlusion.<sup>622</sup> However, such perfusion defects do not distinguish between acute ischemia, acute infarction, or previous infarction. Serial changes on follow-up perfusion images with either <sup>201</sup>Tl or <sup>99m</sup>Tc sestamibi suggest an acute process but still do not distinguish between ischemia or infarction.

**Table 11.** Uses of Radionuclide Testing in Acute Myocardial Infarction

Indication	Diagnosis		Indication	Risk Assessment	
	Test	Class		Test	Class
1. RV infarction	Rest RNA	IIa	1. Residual ischemia	Stress (exercise/pharmacological) thallium with redistribution	I
	$^{99m}$ Tc pyrophosphate	IIa		Stress (exercise/pharmacological) sestamibi with redistribution	
2. Infarction not diagnosed by standard means—early presentation with successful reperfusion	Rest myocardial perfusion imaging	IIb	2. Myocardial infarct size	Tomographic thallium	IIa
	$^{99m}$ Tc pyrophosphate	IIb		Tomographic sestamibi	IIa
3. Infarction not diagnosed by standard means—late presentation	$^{99m}$ Tc pyrophosphate	IIa	3. Hibernating myocardium	Early, late thallium	IIa
	Any technique	III		4. Ventricular function	RNA
4. Routine diagnosis					I

RV indicates right ventricular; RNA, radionuclide angiography;  $^{99m}$ Tc, technetium 99m. From the ACC/AHA task force. Guidelines for clinical use of cardiac radionuclide imaging: report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. *J Am Coll Cardiol* 1995;25:521-547.

### Measurement of Infarct Size

Technetium 99m sestamibi is uniquely suited to accurate measurement of myocardium at risk in clinical infarction. Because there is minimal redistribution of the radiopharmaceutical over time, imaging can be delayed for several hours after injection and still provide accurate information about myocardial perfusion at the time of injection. The validity and feasibility of this approach has been well established in animal and clinical studies.<sup>623-626</sup>

As mentioned previously, myocardium at risk is a major determinant of final infarct size. However, final infarct size may be considerably smaller than the initial myocardium at risk, reflecting the effects of reperfusion therapy, spontaneous reperfusion, and collateral blood flow.<sup>627</sup> Clinical data have demonstrated the importance of final infarct size as a major determinant of subsequent patient survival and quality of life. Radionuclide techniques are clearly useful for this purpose. In patients who have not received reperfusion therapy, measurement of rest ejection fraction and end-systolic volume index before hospital discharge by equilibrium-gated radionuclide angiography is highly associated with subsequent patient outcome.<sup>613,628</sup> In patients who have received reperfusion therapy, the postdischarge rest ejection fraction by equilibrium radionuclide angiography after resolution of myocardial stunning and compensatory hyperkinesia is highly associated with subsequent patient outcome.<sup>596,629,630</sup>

Myocardial perfusion imaging with  $^{201}$ Tl and  $^{99m}$ Tc sestamibi can also be used to assess infarct size.<sup>596,631,632</sup> Most recently  $^{99m}$ Tc sestamibi has been used with tomographic imaging for this purpose.<sup>633,634</sup> Measurement of infarct size with  $^{99m}$ Tc sestamibi has been closely correlated with other measurements of infarct size, including ejection fraction,<sup>635</sup> regional wall motion score,<sup>635</sup> creatine kinase release,<sup>626</sup> and  $^{201}$ Tl defect size.<sup>632</sup> Two studies have now shown an association between infarct size and patient outcome.<sup>596,597</sup> Table 11 summarizes the uses for radionuclide testing in acute MI.

### Summary of Stress Testing After Acute Myocardial Infarction

It is the consensus of the task force that the current approach to risk stratification of patients after MI requires little change from the recommendations outlined in the original ACC/AHA task force report "Early Management of Patients With Acute Myocardial Infarction." Patients who have clinically declared themselves to be at high risk should have coronary arteriography to identify those who are candidates for revascularization.<sup>97</sup> Patients without clinical complications after infarction should have a submaximal exercise stress test before discharge or, alternatively, a symptom-limited stress test 3 weeks after discharge. Patients who can achieve at least 5 METs are treated medically. If there are signs of severe ischemia at a low level of exercise, such as marked ST-segment change or inability to complete stage I, failure to achieve 3 to 4 METs, or if blood pressure falls during exercise, the patient should undergo coronary arteriography.

It must be acknowledged, however, that the positive predictive value of virtually all noninvasive tests has declined as late prognosis improves, particularly those relatively highly selected patients who have received reperfusion therapy. The paradigm for the future will be a new database that examines the benefits, cost-effectiveness, and incremental value of noninvasive tests among lower-risk patients who have received reperfusion therapy.

In patients for whom the resting ECG is uninterpretable because of BBB, major ST-T wave abnormalities, or digitalis therapy, radionuclide myocardial perfusion imaging with exercise or stress echocardiography should be performed, depending on local experience and expertise. In the patient who cannot exercise, pharmacological stress agents can be used with either myocardial perfusion imaging or echocardiography. It is the view of the committee that exercise electrocardiography is a valuable test in assessing prognosis in patients with coronary artery disease. It is generally available, with experi-

enced personnel capable of performing it safely, and it is relatively inexpensive. After uncomplicated MI, patients can be divided into relatively high- and low-risk groups for subsequent cardiac events if all the information available on the treadmill test is used (Fig 10).

### Ambulatory Electrocardiographic Monitoring for Ischemia

The value of ambulatory electrocardiographic monitoring in assessing reversible myocardial ischemia and the risk of a subsequent coronary event early after myocardial infarction have been evaluated in a number of studies.<sup>636-643</sup> Up to one quarter of patients will show residual ischemia as detected by ambulatory electrocardiographic monitoring. Most episodes of transient myocardial ischemia are silent and occur at rest or during times of low-level physical activity or mental stress.<sup>644</sup> During long-term follow-up studies, a number of investigators have reported that the presence of ischemia detected by ambulatory electrocardiographic monitoring in the postinfarction period is predictive of a subsequent poor outcome and increases the risk of cardiac events.<sup>636-643</sup> One recent study found that the odds ratio for the patients with, as compared to those without, ambulatory ischemia was 2.3 for death or nonfatal MI at 1 year.<sup>643</sup>

Despite the promising initial results with ambulatory electrocardiographic monitoring, the totality of evidence does not support a general statement about its role in all postinfarction patients. Some studies have shown that the results of ambulatory electrocardiographic monitoring could be predicted from exercise test data,<sup>638,640</sup> while others have found that additional prognostic information could be obtained by ambulatory electrocardiographic monitoring in postinfarction patients.<sup>639</sup> At present a cost-effective strategy has not been developed to identify patients who are at increased risk for ambulatory ischemia and in whom ambulatory electrocardiographic monitoring might be more helpful for stratification into high- and low-risk subgroups for future coronary events.

### Assessment of Ventricular Arrhythmia (Signal-Averaged Electrocardiography, Ambulatory [Holter] Monitoring, Heart Rate Variability)

#### Recommendations for Routine Testing

##### **Class I**

None.

##### **Class IIa**

None.

##### **Class IIb**

1. Ambulatory (Holter) monitoring, signal-averaged ECG, heart rate variability, baroreflex sensitivity monitoring, alone or in combination with these or other tests, including functional tests (ejection fraction, treadmill testing) for risk assessment after MI, especially in patients at higher perceived risk, when findings might influence management issues, or for clinical research purposes.

The risk of malignant ventricular arrhythmias after hospital discharge is greatest in the first year after acute MI.<sup>645-649</sup> Recent data suggest that thrombolytic therapy reduces this risk and also confirm that LV dysfunction remains an important, although diminished, predictor of mortality, including sudden death.<sup>614,650-653</sup> An open infarct-related artery has emerged as an important predictor of late outcome in other studies.<sup>651</sup> A number of strategies have been used to try to identify patients at high risk for arrhythmic events. Sustained monomorphic VT induced by electrophysiological study is associated with a high arrhythmic event rate<sup>654</sup> but is invasive and has a low specificity. Frequent ventricular premature complexes and higher-grade ventricular ectopy (unsustained VT) on a predischarge Holter monitor also have been associated with a higher mortality among MI survivors, in both the prereperfusion and (less consistently) in the reperfusion eras.<sup>645-653</sup>

Recently, newer techniques, including signal-averaged or high-resolution electrocardiography, heart rate variability, and baroreflex sensitivity, have been used to assess patient risk for sudden cardiac death after MI. Signal-averaged electrocardiography identifies delayed, fragmented conduction in the infarct zone in the form of late potentials at the terminus of the QRS complex and represents an anatomic substrate that predisposes the patient to reentrant VT. Kuchar et al<sup>655</sup> reported late potentials to predict an increased incidence of sudden death in the post-MI patient population. Gomes et al<sup>656</sup> found late potentials to be the best single predictor among Holter monitoring and ejection fraction and contributed independently to a combined index, although the positive predictive value of each was poor. The filtered QRS duration was the most predictive feature of signal-averaged electrocardiography in a CAST substudy.<sup>657</sup> More recent studies have shown reperfusion therapy to reduce the incidence of late potentials after acute MI.<sup>658</sup> In the setting of frequent use of thrombolysis, the predictive value of signal-averaged electrocardiography has been variable.<sup>650-652</sup>

Heart rate variability, an analysis of the beat-to-beat variation in cycle length, largely reflects the sympathovagal interaction regulating heart rate. Heart rate variability can be quantified in a number of ways, using either time or frequency domain parameters.<sup>659</sup> Low heart rate variability, indicative of decreased vagal tone, is a predictor of increased mortality, including sudden death, in patients after MI<sup>659,660</sup> and may add significant prognostic information to other parameters.<sup>660</sup> In one study decreased heart rate variability was more predictive of arrhythmic events than the presence of late potentials, Holter-derived data, treadmill test results, or ejection fraction; reduced heart rate variability and a late potential by signal-averaged electrocardiography was the strongest combined predictor.<sup>652</sup> Standards of measurement, physiological interpretation, and clinical use of heart rate variability have been recently published by a task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.<sup>661</sup> The predictive value of heart rate variability after MI, although significant, is modest when used alone. In combination with other techniques its positive predictive accu-

racy improves. However, the most practical, feasible, and cost-efficient combination of noninvasive predictive tests with heart rate variability remains to be determined.

Baroreceptor sensitivity also quantifies the influence of parasympathetic tone on the heart. Baroreceptor sensitivity is measured as the slope of a regression line relating beat-to-beat heart rate change in response to a change in blood pressure, often accomplished by giving a small bolus of phenylephrine.<sup>662</sup> Acute MI-associated reductions in baroreflex sensitivity have been associated with an increased susceptibility to arrhythmic events and sudden death in experimental models and initial clinical reports<sup>663-665</sup> and are being further characterized in a multicenter prospective post-MI study (Autonomic Tone and Reflexes After Myocardial Infarction [ATRAMI]).

### **Summary/Conclusions**

Although several investigators have reported an increased likelihood of arrhythmic events in patients when one or more noninvasive test is abnormal, two important caveats prevent these techniques from being recommended for routine clinical practice at present. First, although the negative predictive value of most of these tests taken in isolation is high (generally greater than 90%), the positive predictive value is unacceptably low (less than 30%). Second, although the positive predictive value of noninvasive testing for future arrhythmic events can be modestly increased by combining several test results, the therapeutic implications of positive findings are unclear. Insufficient data are available to indicate whether general therapies, such as  $\beta$ -adrenoceptor blockade, ACE inhibition, and revascularization procedures, or specific interventions, such as treatment with amiodarone or an implantable cardioverter-defibrillator, targeted for high-risk patients identified by a combination of noninvasive tests after MI can more favorably impact mortality.<sup>666</sup> Moreover, it is difficult to justify the costs of the routine use of these procedures in the absence of therapeutic guidelines or demonstrated clinical benefits associated with a positive test. Until these issues are resolved, use of these tests cannot be recommended in routine management, although they will continue to be of interest as investigational tools for specific risk-assessment protocols.

### **Invasive Evaluation**

#### **Coronary Angiography and Possible Percutaneous Transluminal Coronary Angioplasty After Myocardial Infarction**

#### **Recommendations**

##### **Class I**

1. Patients with spontaneous episodes of myocardial ischemia or episodes of myocardial ischemia provoked by minimal exertion during recovery from infarction.
2. Before definitive therapy of a mechanical complication of infarction such as acute mitral regurgitation, VSD, pseudoaneurysm, or LV aneurysm.

#### **3. Patients with persistent hemodynamic instability.**

##### **Class IIa**

1. When MI is suspected to have occurred by a mechanism other than thrombotic occlusion at an atherosclerotic plaque. This would include coronary embolism, certain metabolic or hematological diseases, or coronary artery spasm.

2. Survivors of acute MI with depressed LV systolic function (LV ejection fraction less than or equal to 40%), CHF, prior revascularization, or malignant ventricular arrhythmias.

3. Survivors of acute MI who had clinical heart failure during the acute episode but subsequently demonstrated well-preserved LV function.

##### **Class IIb**

1. Coronary angiography performed in all patients after infarction to find persistently occluded infarct-related arteries in an attempt to revascularize the artery or identify patients with three-vessel disease.

2. All patients after a non-Q wave MI.

3. Recurrent VT or VF or both, despite antiarrhythmic therapy in patients without evidence of ongoing myocardial ischemia.

##### **Class III**

1. Routine use of coronary angiography and subsequent PTCA of the infarct-related artery within days after receiving thrombolytic therapy.

2. Survivors of MI who are thought not to be candidates for coronary revascularization.

This section discusses indications for coronary angiography and possible angioplasty (PTCA) in patients with acute MI. The use of emergency angiography and primary PTCA in evolving acute MI is considered separately from use of PTCA as an adjunct to thrombolytic therapy (see "Initial Recognition and Management in the Emergency Department").

#### **Coronary Angiography in the Survivor of Myocardial Infarction Not Receiving Thrombolytic Therapy**

All survivors of MI who are candidates for revascularization therapy (irrespective of whether they were given thrombolytic therapy) with (1) postinfarction angina, (2) objective evidence of ischemia on stress testing, or (3) noninvasive evidence of LV systolic dysfunction should be considered for coronary angiography, because PTCA or CABG may be considered in these patients if they are found to have significant coronary artery disease.

#### **Coronary Angiography and Possible Percutaneous Transluminal Coronary Angioplasty After Thrombolytic Therapy**

In the immediate period after intravenous administration of thrombolytic therapy, coronary angiography and PTCA have been proposed (1) to restore antegrade coronary flow in the patient in whom thrombolytic therapy is unsuccessful (*adjunctive* PTCA—a term preferred to "rescue") or (2) to reduce the

severity of the residual stenosis of the infarct-related artery in the person in whom thrombolytic therapy is successful.

### Adjuvant Percutaneous Transluminal Coronary Angioplasty

#### Immediately After Failed Thrombolysis

Intravenous thrombolytic therapy successfully restores antegrade coronary flow in 75% to 90% of patients with acute MI.<sup>66,67</sup> In those in whom it is unsuccessful, antegrade coronary flow can usually be restored with PTCA. Several studies have demonstrated the marked beneficial effect of infarct-related artery patency (obtained via endogenous, pharmacological, or mechanical recanalization) on survival in patients with acute MI.<sup>50,66,68</sup> Survivors of infarction with a patent infarct-related artery demonstrated at 90 minutes after treatment have an improved long-term outcome when compared with those with an occluded infarct-related artery, even when LV systolic function is similar.<sup>66,670</sup> Therefore, in patients in whom thrombolytic therapy fails to restore antegrade coronary flow, recanalization of the infarct-related artery via PTCA has been advocated to (1) establish early infarct-related artery patency, (2) salvage ischemic (but viable) myocardium, and (3) improve long-term survival. Only one relatively small randomized trial<sup>671</sup> has assessed the effects of early (performed immediately after identification of failed thrombolysis) adjuvant PTCA on LV function, subsequent cardiac events, or mortality. The results showed a trend favoring better outcomes in those assigned to adjuvant PTCA, but the high mortality rate associated with failed PTCA in this setting and the lack of statistical power of the study argue against its routine use.

A major problem in adopting a strategy of adjuvant PTCA lies in the limitation of accurate identification of patients in whom thrombolytic therapy has not restored antegrade coronary flow. Unless unsuccessful thrombolysis is recognized and corrected quickly (within 3 to 6 hours of onset of symptoms), salvage of ischemic myocardium is unlikely. Unfortunately, clinical markers of reperfusion, such as relief of ischemic-type chest discomfort, resolution of ST-segment elevation, and reperfusion arrhythmias, have limited predictive value in identifying failure of thrombolysis.<sup>672</sup> Immediate catheterization of all patients following thrombolytic therapy to identify those with an occluded infarct-related artery is impractical, costly, and often associated with bleeding complications.<sup>673,674</sup>

Even in the patient with documented failure of thrombolysis, it is unknown if adjuvant PTCA should be attempted. First, because extensive myocardial necrosis occurs when coronary occlusion has been present for more than 3 hours,<sup>449</sup> PTCA may not salvage a substantial amount of myocardium, considering the time delay associated with presentation of the patient to the hospital after onset of symptoms, infusion of the thrombolytic agent, recognition of failed thrombolysis, and subsequent initiation of PTCA. Second, adjuvant PTCA fails to reestablish antegrade coronary flow in about 10% of patients, and reocclusion of the infarct-related artery occurs in as many as 20% of the remainder.<sup>675</sup> Third, unsuccessful salvage PTCA is associated with a high mortality.<sup>237,238</sup> Finally, coro-

nary reperfusion occurs over the subsequent hours in many patients with an infarct-related artery that occluded early after thrombolytic therapy. Although infarct-related artery patency is only 65% to 75% 90 minutes after thrombolytic therapy, it rises to 90% by 24 hours.<sup>667</sup> Such "late" reperfusion may improve survival without the risk of invasive procedures coupled with thrombolytic therapy.

Recent nonrandomized and retrospective studies have suggested that mechanical reperfusion of occluded coronary arteries may improve survival in patients with MI and cardiogenic shock.<sup>238</sup> Such patients have an in-hospital survival rate ranging from 20% to 50% when treated with intravenous thrombolytic therapy.<sup>292</sup> Mechanical restoration of antegrade coronary flow via PTCA can be associated with a hospital survival rate ranging from 40% to 70%. Multicenter, prospective, randomized studies are currently under way to objectively test these promising observations.

#### Hours to Days After Failed Thrombolysis

Patency of the infarct-related artery is an important predictor of mortality in survivors of MI.<sup>668,669</sup> In comparison with those with a patent infarct-related artery, survivors of infarction with an occluded artery have (1) increased LV dilatation,<sup>676</sup> (2) a greater incidence of spontaneous and inducible ventricular arrhythmias,<sup>677</sup> and (3) a poorer prognosis.<sup>678</sup> In survivors of infarction, infarct-related artery patency may favorably influence LV remodeling and electrical stability even if accomplished at a time when salvage of ischemic myocardium is unlikely (ie, hours to days after unsuccessful thrombolysis). The usefulness of PTCA of a persistently occluded infarct-related artery 7 to 48 hours after symptom onset was assessed in a relatively small number of patients ( $n=71$ ) in the randomized TAMI-6 Study.<sup>679</sup> Angiography 6 months later revealed a high incidence of infarct-related artery patency in those who did not receive PTCA as well as a high incidence of reocclusion in those who did, so that infarct-related artery patency was similar in the two groups. Not surprisingly, the two groups had similar LV ejection fractions, incidence of reinfarction, hospital readmission, and mortality during follow-up. Although other studies in very small numbers of patients<sup>680</sup> suggested that routine PTCA of occluded infarct-related arteries may improve LV performance, there are no convincing data to support the routine use of adjuvant PTCA within 48 hours of failed thrombolysis.

#### Routine Coronary Angiography and Percutaneous Transluminal Coronary Angioplasty After Successful Thrombolytic Therapy

#### Recommendations

##### *Class I*

None.

##### *Class IIa*

None.

### Class III

1. Routine PTCA of the stenotic infarct-related artery immediately after thrombolytic therapy.
2. Percutaneous transluminal coronary angioplasty of the stenotic infarct-related artery within 48 hours of receiving a thrombolytic agent in asymptomatic patients without evidence of ischemia.

Occlusive coronary thrombus and subsequent MI occur when platelets and fibrin aggregate at sites of endothelial injury or atherosclerotic plaque rupture. For several days after successful fibrinolysis, platelet aggregation and thrombus formation may recur at the site of arterial injury and lead to reocclusion, especially if a severe residual stenosis is present. Hence, many physicians perform catheterization on all patients who have received thrombolysis with the intention of performing PTCA if a high-grade residual stenosis is present to prevent reocclusion, reinfarction, and death. This rationale has led to strategies that include performing PTCA immediately (within hours), early (within 48 hours), or late (up to 2 weeks) after thrombolytic therapy. A number of important clinical trials have addressed each of these strategies, and their findings merit special mention and careful consideration.

#### Immediately After Successful Thrombolysis

Three randomized, prospective trials have examined the efficacy and safety of immediate PTCA after thrombolysis. In the TIMI-IIA study,<sup>673</sup> 389 patients received r-TPA, after which they were randomly assigned to immediate (within 2 hours) or delayed (18 to 48 hours) PTCA of the infarct-related artery. Left ventricular function, the primary end point of the study, was similar for the two groups at hospital discharge and 6 weeks. The incidence of exercise-induced ischemia was similar for both groups. However, those who underwent immediate PTCA had an increased incidence of major adverse events (death, recurrent infarction, emergency CABG surgery, or transfusion). In the TAMI study<sup>674</sup> 197 patients underwent routine PTCA of a stenotic infarct-related artery immediately (90 minutes) or 7 to 10 days after thrombolytic therapy. Left ventricular ejection fraction at 1 week was similar for the two groups, as was incidence of reocclusion. Notably, 18% of the patients required a transfusion of 2 or more units of blood as a result of catheterization. A similar outcome was noted in the European Cooperative Study Group VI trial,<sup>681</sup> in which 367 patients who received thrombolytic therapy were randomly assigned to immediate PTCA or conservative management, with cardiac catheterization and PTCA only for those with spontaneous or provokable ischemia. Immediate PTCA did not influence LV ejection fraction or the subsequent incidence of reinfarction. However, those who underwent immediate PTCA had a higher incidence of recurrent ischemia (17% versus 3%), bleeding complications (41% versus 23%), and transfusions (10% versus 4%). The study was prematurely terminated because those who underwent immediate PTCA had a higher early (2-week) mortality (7% versus 3%). At 1 year the differences in outcome persisted.

Taken together, these trials show no benefit of routine PTCA of the stenotic infarct-related artery immediately after thrombolytic therapy. Such a strategy does not appear to salvage myocardium or prevent reinfarction or death, and those subjected to this approach appear to have an increased incidence of adverse events, including bleeding, recurrent ischemia, emergency CABG, and death.

Recent studies have provided insight into why routine PTCA immediately after thrombolysis may be deleterious. In these patients, vascular complications at the site of catheterization account for most of the excessive bleeding and transfusion requirements. Furthermore, when PTCA is performed after thrombolytic therapy in a patent vessel with some antegrade flow, there is more extensive hemorrhage into the vessel wall than when either treatment is used alone.<sup>682</sup> This may further compromise the lumen of the infarct-related artery and promote rethrombosis and reocclusion.

#### Hours to Days After Successful Thrombolysis

It has been suggested that elective PTCA of the stenotic infarct-related artery hours to days after thrombolysis may allow sufficient time for development of a more stable hemostatic milieu at the site of previous thrombotic occlusion. In this setting PTCA would be safer and more effective in reducing the incidence of reocclusion and improving survival. Two large randomized, prospective trials have tested this hypothesis, with both concluding that (1) there are fewer complications if PTCA is delayed for several days after thrombolytic therapy, and (2) routine PTCA in the absence of spontaneous or provokable ischemia does not improve LV function or survival. In the British SWIFT (Should We Intervene Following Thrombolysis?) Study,<sup>683</sup> 800 patients with acute MI who received intravenous anistreplase were randomly assigned to PTCA within 2 to 7 days or to conservative management with catheterization and PTCA only for spontaneous or provokable ischemia. There was no difference between the two treatment strategies with regard to LV function, incidence of reinfarction, in-hospital survival, or 1-year survival. The TIMI-IIB trial<sup>687</sup> randomly assigned 3262 patients who had received r-TPA to routine catheterization and PTCA within 18 to 48 hours of thrombolysis or conservative management. At the end of the 6-week follow-up period, the two groups had a similar mortality (5.2% versus 4.7%, respectively), incidence of nonfatal reinfarction (6.4% versus 5.8%, respectively), and LV ejection fraction (0.50 versus 0.50, respectively). At 1 and 3 years, survival, anginal class, and frequency of bypass surgery were similar in the two groups.<sup>684,685</sup> Thus, in unselected patients receiving thrombolytic therapy, PTCA of the stenotic infarct-related artery in the absence of evidence of recurrent ischemia within 48 hours does not appear to be beneficial.

It is noteworthy that only recently have data been presented to support the policy of performing catheterization and subsequent revascularization for patients who do have spontaneous or inducible angina after MI. The Danish Acute Myocardial Infarction (DANAMI) Trial<sup>327</sup> randomly assigned 1008 survivors of a first acute MI treated with thrombolytic therapy within

12 hours of onset of symptoms to catheterization and subsequent revascularization or standard medical therapy if they showed evidence of spontaneous or inducible angina. Those who underwent revascularization had less unstable angina and fewer nonfatal MIs during a 2 1/2-year period of follow-up compared with those patients randomly assigned to medical treatment only (18% and 5.6% versus 30% and 10.5%, respectively).

#### *Days to Weeks After Successful Thrombolysis*

Continued clot lysis and remodeling of the infarct-related artery stenosis occurs over the days to weeks after successful thrombolysis, making the underlying residual coronary stenosis more stable and less prone to rethrombosis and reocclusion. Thus, delaying PTCA for days to weeks after thrombolysis might improve survival, even though earlier routine PTCA does not. To date there have not been adequately sized trials to evaluate this treatment strategy. Barbash et al<sup>686</sup> randomly assigned 201 patients treated with tissue plasminogen activator to (1) catheterization and PTCA of suitable lesions, including occluded vessels, more than 72 hours after admission or (2) conservative management with revascularization only for recurrent ischemia. At 10 months the groups had similar LV function, rates of reinfarction, and mortality.

Ellis et al<sup>687</sup> also assessed late PTCA after thrombolytic therapy. Following intravenous thrombolysis, they randomly assigned 87 asymptomatic patients to PTCA at 4 to 14 days or conservative management. Those with postinfarction angina or ischemia with provocative testing were excluded. Although those having PTCA had less angina at 1 year, there was no difference in survival in the two groups. Procedure-related infarction occurred in 9.5% of patients, which is similar to that observed when mechanical revascularization is attempted earlier in the postinfarction course.<sup>688</sup> In short, these relatively small studies have not suggested that routine PTCA in asymptomatic survivors of acute MI is beneficial. It remains to be established whether the more widespread use of IIb/IIIa antiplatelet drugs or intracoronary stents will alter this apparent lack of benefit.

#### **Periprocedural Myocardial Infarction**

A situation meriting special attention is the occurrence of myocardial necrosis in the setting of revascularization procedures. Early surgical literature indicated that although elevation of CK and CK-MB was common during bypass surgery and generally inconsequential, substantial elevations or the development of Q waves<sup>689</sup> have been associated with increased mortality and morbidity. Similarly, elevations of CK-MB are common after percutaneous revascularization procedures. Initial reports indicated no increase in adverse outcomes in patients with elevations less than 50 IU/L,<sup>690</sup> but subsequent reports have indicated a direct relation between CK-MB elevations and both short- and long-term adverse outcomes with no obvious threshold effect.<sup>691,692</sup> A commonsense guideline based on currently available data is to treat patients with an increase in CK-MB more than fivefold in the same manner as any other patient with an MI. Patients with elevations less than threefold above the upper limit

of normal may be discharged from the hospital in a routine manner, although careful follow-up is indicated because of the higher late event rate. Patients with elevations between three and five times normal are in an uncertain category; especially when the elevation is associated with clinically apparent abrupt closure or side branch occlusion, careful monitoring and routine care for patients with myocardial necrosis would be a conservative route. This area needs considerable further research to determine if enzyme elevations have different meanings as a function of the device used and whether the currently observed adverse prognosis is due to the enzyme elevation itself or the underlying severity of illness of the patients.

#### **Secondary Prevention**

##### **Management of Lipids**

##### **Recommendations**

###### *Class I*

1. The AHA Step II diet, which is low in saturated fat and cholesterol (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol), should be instituted in all patients after recovery from acute MI.
2. Patients with LDL cholesterol levels greater than 125 mg/dL despite the AHA Step II diet should be placed on drug therapy with the goal of reducing LDL to less than 100 mg/dL.
3. Patients with normal plasma cholesterol levels who have a high-density lipoprotein (HDL) cholesterol level less than 35 mg/dL should receive nonpharmacological therapy (eg, exercise) designed to raise it.

###### *Class IIa*

1. Drug therapy may be added to diet in patients with LDL cholesterol levels less than 130 mg/dL but greater than 100 mg/dL after an appropriate trial of the AHA Step II diet alone.\*
2. Patients with normal total cholesterol levels but HDL cholesterol less than 35 mg/dL despite dietary and other nonpharmacological therapy may be started on drugs such as niacin to raise HDL levels.

###### *Class IIb*

1. Drug therapy using either niacin or gemfibrozil may be added to diet regardless of LDL and HDL levels when triglyceride levels are greater than 400 mg/dL.

Approximately 70% of coronary heart disease deaths and 50% of MIs occur in patients who have previously established coronary artery disease.<sup>693</sup> It is estimated that the likelihood of fatal and nonfatal MIs is four to seven times higher in patients with apparent coronary disease. Several years ago an overview

\*HMG CoA reductase drugs produce the greatest lowering of LDL cholesterol. Niacin is less effective in lowering LDL, although it is more effective in raising HDL levels. Resins are rarely sufficiently effective to be used alone, but they may be used to supplement lowering LDL with either niacin or HMG CoA reductase drugs. See reference 693.

of secondary prevention trials using both drugs and diet to lower cholesterol demonstrated an approximate 25% reduction in nonfatal and 14% in fatal MIs.<sup>693</sup> Recently the Scandinavian Simvastatin Survival Study<sup>694</sup> reported results in 4444 men and women with coronary heart disease and moderate hypercholesterolemia observed over 5.4 years. Coronary heart disease mortality was reduced by 42% and total mortality by 30% among those receiving simvastatin compared with placebo. It is noteworthy that the relative risk reduction seen in this trial was similar among those with the lowest quartile compared with the highest quartile of serum LDL cholesterol. The Cholesterol and Recurrent events (CARE) trial was a similar study in a population of patients who had recovered from an earlier MI and whose total cholesterol (mean 209 mg/dL) and LDL cholesterol (mean 139 mg/dL) were essentially the same as the average for the general population. In this trial 4159 patients were randomly assigned to either 40 mg of pravastatin a day or placebo. After a median follow-up of 5 years, there was a significant 24% reduction in the primary end point of fatal coronary heart disease and nonfatal confirmed MIs in the pravastatin cohort.<sup>695</sup> These results firmly establish the desirability of lowering atherogenic serum lipids among patients who have recovered from an acute MI.

The effect of cholesterol lowering combined with low-intensity oral anticoagulation on late saphenous vein graft status was also recently reported.<sup>696</sup> In an angiographic trial attempting to reduce atherosclerosis in saphenous vein grafts, post-coronary bypass graft, aggressive lowering of LDL to less than 100 mg/dL with lovastatin, 80 mg daily, in addition to a Step I AHA diet, achieved a significant 29% reduction in obstructive changes in the vein grafts at 4 to 5 years. There was no additional effect of low-dose warfarin in achieving further reduction.

Approximately 25% of patients who have recovered from an MI demonstrate normal total cholesterol but a low HDL cholesterol fraction on a lipid profile. Low HDL cholesterol is an independent risk factor for development of coronary artery disease,<sup>697</sup> and therefore a rationale exists for attempting to raise HDL cholesterol when it is found to be low in the patient with coronary artery disease. The effect of hypertriglyceridemia is more obscure because in many cases the level varies inversely with HDL cholesterol levels. However, if moderate to severe hypertriglyceridemia exists in a patient with established coronary disease, it is probably desirable to attempt to lower triglycerides.

The National Cholesterol Education Panel II has recommended that a complete blood lipid profile be taken in all patients with established coronary heart disease.<sup>698</sup> In the infarct patient, this should be done at the time of admission or no later than the first 24 hours; otherwise, there is a minimum 4-week waiting period after onset of the infarct to allow lipid fractions to stabilize and ensure accuracy. During this interim all patients should be treated with a low-cholesterol, low-saturated fat diet such as the AHA Step II diet. If plasma LDL cholesterol concentrations remain greater than 130 mg/dL, drug therapy should be initiated with the goal of achieving an LDL level less than 100 mg/dL. The drugs available for accomplishing this include HMG CoA reductase

inhibitors, nicotinic acid, and bile acid sequestrants. The use of fibrates in patients with established coronary heart disease should be reserved for patients demonstrating moderate to marked elevations in serum triglycerides as well as low HDL cholesterol. In an adjunct study to the Helsinki Primary Prevention Trial, gemfibrozil given to patients with known or suspected coronary artery disease actually resulted in a trend toward more clinical events than in the control group at the end of 5 years.<sup>699</sup>

Rehabilitation programs stressing nonpharmacological interventions have been shown to achieve significant reductions in total cholesterol levels and LDL, with increases in HDL levels.<sup>700</sup> Exercise, weight management, dietary modification, stress management, and smoking cessation have all been shown to improve blood lipid levels, even without lipid-lowering medications. Because most programs are multifactorial, it is difficult to ascertain which of the treatments are most effective. There are data, however, that demonstrate that exercise and moderate consumption of alcohol can effectively raise HDL levels.<sup>701-703</sup>

According to a policy statement on lipids by the Council on Geriatric Cardiology (personal communication, W. Kannel, March 1996):

Diet and drug treatments available for the correction of lipid abnormalities are as effective in the elderly as in the young. Clinical trials have shown that such treatment can reduce total mortality up to age 70<sup>694</sup> and the rate of recurrent coronary events up to the age 75.<sup>695</sup> In addition, to date, there have been no trials to test the value of lipid control for the prevention of initial coronary events in older persons. Such treatment appears reasonable, however, in those elderly who also have other risk factors such as high blood pressure and diabetes, because their risk of a coronary attack is similar to that of persons who have already survived an attack.

### Smoking Cessation

Smoking cessation is essential in patients with acute MI. Smoking triggers coronary spasm, reduces the anti-ischemic effects of  $\beta$ -adrenoceptor blockers, and doubles mortality after acute MI.<sup>704-706</sup> Smoking cessation reduces rates of reinfarction and death within a year of quitting, but one third to one half of patients with acute MI relapse within 6 to 12 months.<sup>707</sup>

Houston-Miller and Taylor<sup>708</sup> advocate a stepped approach to smoking cessation:

- Provide a firm, unequivocal message to quit smoking.
- Determine if the patient is willing to quit.
- Determine the best quitting method.
- Plan for problems associated with withdrawal.
- Set a quit date.
- Help the patient cope with urges to smoke.
- Provide additional help as needed.
- Follow up by telephone call or visit.

Nicotine gum and patches have been shown to mitigate symptoms of nicotine withdrawal in recovering patients.<sup>709</sup> These agents are not recommended during hospitalization

due to the sympathomimetic effects of the active ingredient, nicotine. However, the dose of nicotine in gums and patches is significantly lower than that found in cigarettes and may be preferable to cigarette smoking if the patient is experiencing acute withdrawal. Clonidine has been shown to be effective in women but not men<sup>710</sup>; the reason for this finding is unclear. Lobeline has not been shown to have any advantage over placebo<sup>711-713</sup> but is again under investigation.

### Long-Term Use of Aspirin

The long-term use of aspirin in the postinfarct patient also results in a significant reduction in subsequent mortality. In six randomized, placebo-controlled trials in which patients were randomly selected between 1 week and 7 years after the initial infarct, meta-analysis reveals a reduction in vascular mortality of 13% among those randomly assigned to aspirin with a reduction in nonfatal reinfarction of 31% and nonfatal stroke of 42%.<sup>714</sup> Although all of these trials involved the use of aspirin in doses ranging from 300 to 1500 mg/d, a recent trial of patients with chronic stable angina pectoris in which aspirin 75 mg/d was used demonstrated a significant reduction of 34% in the primary end point of nonfatal MI and sudden death.<sup>715</sup> This suggests long-term use of aspirin in the postinfarction patient in a dose as low as 75 mg/d can be effective, with the likelihood that side effects can be reduced. Other antiplatelet agents such as sulfapyrazone and dipyridamole have been used in the postinfarct patient, but there is no evidence from these clinical trials that they were any more efficacious than aspirin alone.<sup>716,717</sup> Ticlopidine, an antiplatelet agent that has been effectively used in unstable angina and cerebrovascular disease, has not been studied in major clinical trials involving patients with acute MI.

### Angiotensin Converting Enzyme Inhibitors

The use of ACE inhibitors early in the acute phase of MI has been described earlier. Angiotensin converting enzyme inhibitors are also of value in selected patients who have recovered from an acute infarction through their ability to interfere with ventricular remodeling and thus attenuating ventricular dilatation over time. The clinical result is a lessened likelihood for development of CHF and death. In addition, the likelihood of a recurrent MI may also be reduced.

The expression of tissue ACE within the heart probably arises from vascular endothelium. In the setting of myocardial necrosis and fibrosis, relatively high concentrations of ACE can be found in the myocardium compared with normal ventricular myocardium.<sup>718</sup> These observations, coupled with experience in both the rat model of MI<sup>719</sup> and large randomized clinical trials<sup>720-722</sup> have established that use of ACE inhibitors begun after a patient has recovered from acute MI improves long-term survival, provided the infarct was large, and anterior in location and results in significant impairment of LV contractility. Specifically, in the Survival and Ventricular Enlargement (SAVE) trial, patients received captopril at a mean 11 days after onset of infarction, resulting in an approx-

imate 20% reduction in mortality.<sup>720</sup> The Acute Infarction Ramipril Efficacy (AIRE) trial, in which patients who had been in clinical heart failure during the first day of their infarct and were then randomly assigned an average of 5 days after onset of infarction to either ramipril or placebo, resulted in an approximate risk reduction of 27% in all-cause mortality.<sup>721</sup> Similarly, the Trandolapril Cardiac Evaluation (TRACE) trial, in which patients with LV dysfunction on echocardiogram were randomly assigned to receive either trandolapril or placebo a median 4 days after onset of infarction, demonstrated a 22% reduction in mortality.<sup>722</sup>

The Studies of Left Ventricular Dysfunction (SOLVD) trial evaluated the ACE inhibitor enalapril in 4228 asymptomatic patients with LV ejection fraction less than 0.35, 80% of whom had experienced a prior MI.<sup>723</sup> However, randomization was carried out considerably later on the average than in the SAVE and AIRE trials. This prevention arm of the SOLVD trial revealed a trend toward improved mortality but not a statistically significant difference.<sup>724</sup> On the other hand, SOLVD did demonstrate a significant risk reduction of 20% for the combined end points of death or development of CHF requiring hospitalization.

In secondary analyses of the ACE inhibitor trials, the benefit of treatment appears to be primarily in patients with anterior infarctions or LV ejection fraction below 40%. Some rationale exists for the use of these drugs in all patients after MI, based on the observation in the SAVE trial that the likelihood of recurrent MI was reduced by approximately 25% in treated patients.<sup>720</sup> However, this finding is based on posthoc analysis and is currently being studied in prospective trials. There is also preliminary evidence that patients who express a homozygous deletional form of the ACE gene (dd) have an increased circulating ACE level and are more likely to develop MI than those with the II allele ACE gene.<sup>725</sup> This reasoning is also supported by recent observations that myocardial levels of ACE are also higher in patients expressing the dd gene.<sup>726</sup>

### $\beta$ -Adrenoceptor Blockers

#### Recommendations for Long-Term Therapy in Survivors of Myocardial Infarction

##### Class I

1. All but low-risk patients without a clear contraindication to  $\beta$ -adrenoceptor blocker therapy. Treatment should begin within a few days of the event (if not initiated acutely) and continue indefinitely.

##### Class IIa

1. Low-risk patients without a clear contraindication to  $\beta$ -adrenoceptor blocker therapy.

##### Class III

1. Patients with a contraindication to  $\beta$ -adrenoceptor blocker therapy.

Several placebo-controlled trials, involving a total of more than 35 000 survivors of MI not receiving thrombolytic therapy, have shown that chronic  $\beta$ -adrenoceptor blocker therapy reduces mortality through a reduction in incidence of sudden and nonsudden cardiac death. Of the available  $\beta$ -adrenoceptor blockers, propranolol,<sup>727</sup> timolol,<sup>728</sup> and metoprolol<sup>729</sup> have been shown to be efficacious in this regard. For example, in the Norwegian trial of timolol conducted in the late 1970s in survivors of infarction, mortality was reduced from 9.8% in those given placebo to 7.2% in those receiving timolol, 10 mg twice daily, over an average observation period of 25 months. Interestingly, the beneficial influence of timolol on survival was sustained for at least 6 years after initiation.<sup>730</sup> Propranolol, 80 mg 3 times daily, and metoprolol, 100 mg twice daily, reduced mortality by 26% and 36%, respectively, in other studies.<sup>727,729</sup>

The salutary effect of long-term  $\beta$ -adrenoceptor blocker therapy is greatest in high-risk patients, ie, those with evidence of large or anterior infarction, and there is continued debate about whether low-risk subjects (ie, those without the following: previous infarction, anterior infarction, advanced age, complex ventricular ectopy, or hemodynamic evidence of LV systolic dysfunction) should be treated with  $\beta$ -adrenoceptor blockers because their long-term prognosis is extremely favorable irrespective of such therapy. Although adverse effects of  $\beta$ -adrenoceptor blockers, such as fatigue, depression, sexual dysfunction, nightmares, and difficulty with recognition of hypoglycemia in diabetics are known to occur, the frequency and severity of these effects are sufficiently low to warrant their use even in low-risk patients. Although no study has determined if long-term  $\beta$ -adrenoceptor blocker therapy should be administered to survivors of MI who subsequently have successfully undergone revascularization, there is no reason to believe that these agents act differently in coronary patients who have undergone revascularization.

### Antioxidants

Earlier observational data from epidemiological studies suggest that an increased intake of lipid-soluble antioxidant vitamins (vitamin E and beta carotene) is associated with reduced rates of cardiovascular events, including acute MI.<sup>731-733</sup> In support of these data, one randomized placebo control study of vitamin E treatment in 2002 patients with documented coronary disease indicated a 77% reduction in nonfatal MI but no effect on cardiovascular death or overall mortality.<sup>734</sup> However, a mid-study change in the vitamin E dose and some imbalance in the use of  $\beta$ -adrenoceptor blockers in subjects receiving vitamin E make interpretation of that study problematic. A recent prospective cohort study of over 34 000 postmenopausal women indicated that an increase in dietary vitamin E but not supplemental vitamin E was associated with decreased cardiovascular risk.<sup>735</sup> Regarding beta carotene, several prospective studies have convincingly shown a lack of beneficial effect on cardiovascular disease,<sup>736-738</sup> and two studies have indicated an increase in lung cancer with beta-carotene treatment.<sup>736,737</sup>

There is even less evidence to support the use of water-soluble enzymatic antioxidants for cardiovascular disease. Although one study suggested reduced cardiovascular risk in subjects on supplemental vitamin C,<sup>739</sup> the majority of other large epidemiological studies have not indicated a benefit.<sup>731-733</sup> Thus, routine use of vitamin C cannot be recommended.

Despite promising experimental studies, recombinant superoxide dismutase failed to reduce infarct size in a well-controlled acute PTCA trial.<sup>740</sup> One small study showed a trend for reduced restenosis with vitamin E treatment following coronary angioplasty (restenosis rate 35.5% for treatment group versus 47.5% placebo; n=100, P=.06).<sup>741</sup> A larger study evaluating the combination of vitamin E in association with  $\omega$ -3 fatty acids 2 weeks before elective PTCA showed no impact on the restenosis rate.<sup>742</sup>

Thus, there is no convincing evidence to support lipid- or water-soluble antioxidant supplementation in patients after MI or patients with or without established coronary disease. Because these agents are not harmless, the growing practice of recommending antioxidant supplements in these patients should be discouraged until the results of ongoing, well-controlled studies become available and unequivocally indicate a beneficial effect.

### Anticoagulants

#### Recommendations for Long-Term Anticoagulation After Acute Myocardial Infarction

##### *Class I*

1. For secondary prevention of MI in post-MI patients unable to take daily aspirin.\*
2. Post-MI patients in persistent AF.
3. Patients with LV thrombus.

##### *Class IIa*

1. Post-MI patients with extensive wall motion abnormalities.
2. Patients with paroxysmal AF.

##### *Class IIb*

1. Post-MI patients with severe LV systolic dysfunction with or without CHF.

The indications for long-term anticoagulation after acute MI remain controversial. A series of studies comparing warfarin with conventional therapy has demonstrated a reduction in risk of death of 13% and reduction in relative risk of both stroke and reinfarction of 41%.<sup>743</sup> The lack of aspirin use in the control groups in these trials has made it difficult to assess the relative merits of aspirin alone versus warfarin alone. Although a cost-effectiveness analysis demonstrates that warfarin compared with standard therapy without aspirin meets the general criteria for cost-effective therapy, the more impressive cost-effectiveness of aspirin<sup>744</sup> makes aspirin alone the current

\*See section on "Aspirin," page 1344.

standard antithrombotic regimen for secondary prevention. Although an ample theoretical rationale can be developed for using aspirin and warfarin in combination as a secondary preventive strategy, inadequate empirical information currently exists to recommend it at this time. In a recent report evaluating 160 mg aspirin versus 80 mg aspirin plus 3 mg warfarin versus 80 mg aspirin plus 1 mg warfarin, there was no evidence that combined low-dose aspirin and warfarin reduced subsequent events in 8800 patients after MI. Thromboembolic stroke rates tended to be higher in low-dose warfarin-treated patients as well.<sup>745</sup>

The previous ACC/AHA guidelines strongly recommended the use of oral anticoagulants with an International Normalized Ratio (INR) ratio of 2.0 to 3.0 in patients with a ventricular mural thrombus or a large akinetic region of the left ventricle for at least 3 months. Despite a number of small observational studies demonstrating a higher risk of embolic stroke in patients with large anterior infarction and a better outcome in patients treated with warfarin after demonstration of LV mural thrombus by echocardiography,<sup>746</sup> randomized controlled trials are not available to support this recommendation. Concern exists that patients at lower risk were treated in the observational studies, so that a firm recommendation based on empirical information cannot be made. Warfarin is indicated in patients with persistent AF after MI, based on results of multiple trials in other patients with AF.

### Calcium Channel Blockers

Calcium channel blockers are not presently recommended for routine treatment or secondary prevention after acute MI. In general, calcium channel blockers should be reserved to treat the subset of patients with angina or hypertension inadequately controlled by other agents. If  $\beta$ -adrenoceptor blockers are contraindicated or poorly tolerated, calcium antagonists that slow heart rate (such as verapamil or diltiazem) may be appropriate as an alternative for secondary prevention in those patients with preserved LV function.<sup>230,311,532,538,542,747-755</sup>

### Estrogen Replacement Therapy and Myocardial Infarction

The issue of estrogen replacement therapy (ERT) for cardiovascular disease in women is far from clear. Observational studies<sup>756,757</sup> have been interpreted as indicating that oral unopposed estrogen is effective in primary prevention of cardiovascular disease. Confounding factors such as compliance<sup>758</sup> and baseline health in these studies make it difficult to be certain of the effect of ERT.

Recent clinical trials have shown that estrogen given alone or in combination with progestin improves the lipid profile and lowers fibrinogen.<sup>759</sup> Favorable effects of estrogen on the lipid profile would, theoretically, be expected to produce a favorable result in preventing coronary atherosclerosis. There is concern

that combining estrogen with a progestin<sup>760</sup> will ameliorate the potential beneficial effect of ERT on the lipid profile.

In 1993 the American Heart Association and the American Fertility Society sponsored a consensus conference on postmenopausal hormone therapy and the cardiovascular system.<sup>761</sup> This conference concluded that the limited data available would indicate that estrogen therapy did reduce mortality in women with moderate and severe coronary artery disease.

Other factors must be considered in recommending ERT. These include beneficial effects on osteoporosis, sexuality, skin tone, and psychological well-being. These must be weighed against the concern of the possible increase in breast cancer rates, although this is highly controversial.<sup>762,763</sup> A hypothetical population-based analysis by Gorsky et al<sup>764</sup> concluded that there was a health benefit of ERT that exceeded any risk.

The dose of estrogen for postmenopausal women who have had a hysterectomy is usually 0.625 mg oral conjugated estrogen or its equivalent once a day. In postmenopausal women with a uterus, two dosing schedules are commonly used: 0.625 mg conjugated estrogen or its equivalent once a day plus 10 mg progestin (medroxy-progesterone) orally per day for 10 to 14 days each month or 2.5 mg progestin orally every day. Screening procedures for women without a uterus who are taking estrogen are no different than for the nontreated population. If women receiving cyclic progestins develop bleeding other than at time of withdrawal, or women receiving continuous progestin develop either heavy, prolonged, frequent, or intermittent bleeding lasting longer than 10 months after the start of progestin, they should be evaluated for the bleeding.<sup>765</sup>

Given the overall uncertainty about the true benefit of ERT in a woman after MI, patient preference is the dominant factor in making any decision. Estrogen replacement therapy is most likely of benefit in both primary and secondary prevention of coronary artery disease.

### Recommendation

#### *Class IIa*

1. All postmenopausal patients who have an MI should be carefully counseled about the potential beneficial effects of ERT and offered the option of ERT if they desire it.

### Antiarrhythmic Agents

Given the risks of traditional (Class I) antiarrhythmic therapy as observed in CAST, a study that tested suppressive antiarrhythmic therapy targeted to patients with frequent and complex ventricular ectopy,<sup>2</sup> there is little support at present for the hypothesis that suppression of premature ventricular complexes in post-MI patients will lower mortality. Routine ambulatory (Holter) monitor recordings to identify patients who should receive antiarrhythmic therapy at the time of discharge after an MI is therefore not presently indicated.

Amiodarone, a drug with Class III (as well as Class I, II, and IV action) has shown promise in some but not all post-MI pilot studies.<sup>766-768</sup> These potential benefits of empiric therapy with amiodarone after MI were tested recently in two moderate-size randomized trials involving post-MI patients at high risk due to LV dysfunction (European Myocardial Infarction Amiodarone Trial [EMIAT]) or ventricular arrhythmias (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial [CAMIAT]). In preliminary reports presented at the 1996 ACC Scientific Session, amiodarone appeared to reduce arrhythmia death and cardiac arrest, but effects on total mortality were not significant. Also, tolerance of long-term amiodarone was poor (40% dropout rate). Thus, amiodarone is safe to use after MI, if necessary for suppression of severe, symptomatic arrhythmias, but  $\beta$ -adrenoceptor blocker therapy is preferred for general prophylaxis.

## VII. Long-Term Management

The majority of patients need to modify their lifestyle after acute MI. Typical recommendations require a change in previous behavior, including exercise, diet, smoking cessation, stress management, and medication adherence. Achievement of these goals is often complicated by denial of the significance of the event, physical deconditioning that may reflect a lifelong history of sedentary behavior, and emotional distress. Achievement of treatment goals may be facilitated through participation in a formal cardiac rehabilitation program or home rehabilitation if the patient is sufficiently motivated.

### *Cardiac Rehabilitation*

Cardiac rehabilitation combines prescriptive exercise training with education about coronary risk factor modification techniques. Formal rehabilitation programs have been shown to effectively improve functional capacity,<sup>769</sup> promote compliance, decrease emotional distress, improve quality of life, reduce cardiovascular mortality,<sup>770</sup> mitigate ischemic symptoms,<sup>771</sup> promote reversal of atherosclerosis,<sup>772</sup> and reduce risk of subsequent coronary events.<sup>773</sup> Cardiac rehabilitation may decrease denial, which is known to have a repressive effect and may discourage treatment compliance and recovery after discharge.<sup>774</sup>

Despite these benefits, only 15% of qualified patients participate in cardiac rehabilitation, possibly because of lack of physician referral, poor motivation, logistical or financial constraints, or a combination of these factors.<sup>775</sup> Home exercise training programs have been shown to be beneficial in certain low-risk patient groups.<sup>776</sup> They offer the advantages of convenience and low cost but lack the valuable elements of education and group interaction.

Social integration and social support have been repeatedly shown to influence outcomes after acute MI. Social integration refers to existence of social ties (eg, spouse, close family

members, or friends) and degree of participation in group activities (eg, family gatherings, religious affiliations). Social support refers to the actual or perceived receipt of information, materials, and/or emotional support.

Mortality from all causes, including ischemic heart disease, is lower in socially integrated individuals.<sup>777</sup> Recurrent cardiac events are also significantly lower among persons reporting high levels of social integration when compared with socially isolated persons.<sup>778,779</sup>

The most effective social support interventions occur naturally. Family members should be told the importance of their support, including the observation that the need for support has been shown to last longer than most family members realize.<sup>780</sup> The quality of the support provided is key; support has been shown to facilitate treatment compliance but only when "policing" is minimized.<sup>781</sup> Telephone follow-up, cardiac rehabilitation, or other group events can be effective methods of support for socially isolated individuals.<sup>708</sup> Family members should be offered the opportunity to learn CPR because most episodes of cardiac arrest occur within 18 months after hospital discharge for acute MI.<sup>187</sup>

### *Return to Prior Levels of Activity*

A significant percentage (14%) of the estimated \$56 billion cost to society of coronary artery disease in 1994 was due to lost productivity from temporary or permanent disability.<sup>782</sup> Return-to-work rates, which currently range from 63%<sup>783</sup> to 94%,<sup>784</sup> are difficult to influence because they are confounded by factors such as job satisfaction, financial stability, and company policies. Return to prior levels of activity is a better outcome indicator than return to paid employment.

The majority of patients who remain asymptomatic after an uncomplicated acute MI can very likely return to prior activities safely within 2 weeks, although few data are available to guide this recommendation. In PAMI-II a study of primary PTCA in low-risk patients with acute MI (ie, age less than 70 years, ejection fraction greater than 45%, one- or two-vessel disease, good PTCA result), patients were encouraged to return to work at 2 weeks. The actual timing of return to work was not reported, but no adverse events occurred as a result of this strategy.<sup>785</sup> In patients who desire to return to physically demanding activities early, the safety of activity can be determined by comparing performance on a graded exercise test with the MET level required for the desired activity. Table 12 presents energy levels, expressed in METs, required to perform a variety of common activities. This and similar tables can be helpful in translating a patient's performance on a graded exercise test into daily activities that may be undertaken with reasonable safety.

The physician should provide explicit advice about when to return to previous levels of physical activity, sexual activity, and employment. Daily walking can be encouraged immediately.<sup>786</sup> In stable patients without complications (Class I), sexual activity with the usual partner can be resumed within a week to

**Table 12.** Energy Levels Required to Perform Some Common Activities

<3 METs	3-5 METs	5-7 METs	7-9 METs	>9 METs
Self-care				
Washing	Cleaning windows	Easy digging in garden	Sawing wood	Carrying loads upstairs
Shaving	Raking	Level hand lawn mowing	Heavy shoveling	(objects >90 lb)
Dressing	Power lawn mowing	Climbing stairs (slowly)	Climbing stairs	Climbing stairs (quickly)
Desk work	Bedmaking/stripping	Carrying objects (30-60 lb)	(moderate speed)	Shoveling heavy snow
Washing dishes	Carrying objects (15-30 lb)	Digging vigorously	Carrying objects (60-90 lb)	
Driving auto				
Light housekeeping				
Occupational				
Sitting (clerical/assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Lumber jack
Typing		Shoveling dirt		Heavy laborer
Desk work	Auto repair	Sawing wood		
Standing (store clerk)	Light welding/carpentry	Operating pneumatic tools		
Recreational				
Golf (cart)	Dancing (social)	Badminton (competitive)	Canoeing	Handball
Knitting	Golf (walking)	Tennis (singles)	Mountain climbing	Squash
Hand sewing	Sailing	Snow skiing (downhill)	Paddle ball	Ski touring
	Tennis (doubles)	Light backpacking		Vigorous basketball
	Volleyball (6 persons)	Basketball		
		Football		
		Stream fishing		
Physical conditioning				
Walking (2 mph)	Level walking (3-4 mph)	Level walking (4.5-5.0 mph)	Level jogging (5 mph)	Running (>6 mph)
Stationary bike	Level biking (6-8 mph)	Bicycling (9-10 mph)	Swimming (crawl stroke)	Bicycling (>13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Rope jumping
			Heavy calisthenics	Walking uphill (5 mph)
				Bicycling (12 mph)

METs indicates metabolic equivalents. Adapted from Table 9.2, p 147. Rehabilitation of the coronary patient (Wenger NL, Hellerstein HK, eds). Haskell WL. *Design and Implementation of Cardiac Conditioning Program*. New York, NY: Churchill Livingstone; 1978.

10 days. Driving can begin a week after discharge if the patient is judged to be in compliance with individual state laws. Each state's Department of Motor Vehicles or its equivalent has mandated certain criteria that vary from state to state and must be met before operation of a motor vehicle after serious illness.<sup>787</sup> These include such caveats as the need to be accompanied, to avoid stressful circumstances such as rush hour, inclement weather, night driving, heavy traffic, and high speeds. Because commercial aircraft are pressurized to only 7500 to 8000 feet (personal communication, Federal Aviation Administration, February 14, 1996), air travel should be undertaken only by stable patients (without a fear of flying) within the first 2 weeks and then only as long as they travel with companions, carry sublingual nitroglycerin, and request airport transportation to avoid rushing.

For patients who have experienced a complicated MI (requiring CPR, experiencing hypotension, serious arrhythmias, high-degree block, or CHF), driving should be delayed 2 to 3 weeks after symptoms have resolved. Unstable or symptomatic patients or patients with complications should also be stabilized for at least 2 weeks before commercial air travel because of the lowered oxygen tension experienced above 5000 feet.

## Staff

### American College of Cardiology

David J. Field, Executive Vice President  
Grace D. Ronan, Assistant Director, Clinical Practice and Guidelines  
Nelle H. Stewart, Document/Guidelines Coordinator, Clinical Practice and Guidelines  
Helene B. Goldstein, MLS, Director, Griffith Resource Library  
Gwen C. Pigman, MLS, Assistant Director, Griffith Resource Library  
David P. Bodycombe, ScD, Director, Research and Information Management

### American Heart Association

Office of Scientific Affairs  
Rodman D. Starke, MD, FACC, Senior Vice President  
William H. Thies, PhD, Science Consultant

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## References

- Gunnar RM, Bourdillon PDV, Dixon DW, et al. Guidelines for the early management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee to Develop Guidelines for the Early Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 1990;16:249-252.
- Epstein AE, Hallstrom AP, Rogers WJ, et al. Mortality following ventricular arrhythmia suppression by encainide, flecainide, and moricizine after myocardial infarction: the original design concept of the Cardiac Arrhythmia Suppression Trial (CAST). *JAMA* 1993;270:2451-2455.
- Herlitz J, Blohm M, Hartford M, Hjalmarsson A, Holmberg S, Karlson BW. Delay time in suspected acute myocardial infarction and the importance of its modification. *Clin Cardiol* 1989;12:370-374.
- National Heart, Lung, and Blood Institute. *Morbidity and Mortality: Handbook on Cardiovascular, Lung, and Blood Diseases*. Bethesda, Md: US Department of Health and Human Services, Public Health Service, National Institutes of Health; May 1992.
- Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy: the Myocardial Infarction Triage and Intervention Trial. *JAMA* 1993;270:1211-1216.
- Koren G, Weiss AT, Hasin Y, et al. Prevention of myocardial damage in acute myocardial ischemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985;313:1384-1389.
- Hermens WT, Willems GM, Nijssen KM, Simoons ML. Effect of thrombolytic treatment delay on myocardial infarct size. *Lancet* 1992;340:1297. Letter.
- National Heart, Lung, and Blood Institute. *9-1-1: Rapid Identification and Treatment of Acute Myocardial Infarction*. Bethesda, Md: US Department of Health and Human Services, Public Health Service, National Institutes of Health; May 1994. NIH Publication 94-3302.
- National Heart, Lung, and Blood Institute. *Patient/Bystander Recognition and Action: Rapid Identification and Treatment of Acute Myocardial Infarction. National Heart Attack Alert Program (NHAAP)*. Bethesda, Md: National Institutes of Health; 1993. NIH Publication No. 93-3303.
- Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. *Am Heart J* 1984;108:150-158.
- Alonzo AA. The impact of the family and lay others on care-seeking during life-threatening episodes of suspected coronary artery disease. *Soc Sci Med* 1986;22:1297-1311.
- Reilly A, Dracup K, Dattolo J. Factors influencing prehospital delay in patients experiencing chest pain. *Am J Crit Care* 1994;3:300-306.
- Ho MT, Eisenberg MS, Litwin PE, Schaeffer SM, Damon SK. Delay between onset of chest pain and seeking medical care: the effect of public education. *Ann Emerg Med* 1989;18:727-731.
- Liberthson RR, Nagel EL, Hirschman JC, Nussenfeld SR, Blackbourne BD, Davis JH. Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death. *Circulation* 1974;49:790-798.
- Becker LB, Ostrander MP, Barrett J, Kondos GT. Outcome of CPR in a large metropolitan area—where are the survivors? *Ann Emerg Med* 1991; 20:355-361.
- Becker LB, Han BH, Meyer PM, et al. Racial differences in the incidence of cardiac arrest and subsequent survival: the CPR Chicago Project. *N Engl J Med* 1993;329:600-606.
- Lombardi G, Gallagher J, Gennis P. Outcome of out-of-hospital cardiac arrest in New York City: the Pre-Hospital Arrest Survival Evaluation (PHASE) Study. *JAMA* 1994;271:678-683.
- Eisenberg MS, Horowicz BT, Cummins RO, Reynolds-Haertle R, Hearne TR. Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med* 1990;19:179-186.
- Cummins RO, Eisenberg MS, Litwin PE, Graves JR, Hearne TR, Hallstrom AP. Automatic external defibrillators used by emergency medical technicians: a controlled clinical trial. *JAMA* 1987;257:1605-1610.
- Hossack KF, Hartwig R. Cardiac arrest associated with supervised cardiac rehabilitation. *J Cardiac Rehabil* 1982;2:402-408.
- Kerber RE. Statement on early defibrillation: from the Emergency Cardiac Care Committee, American Heart Association. AHA Medical/Scientific Statement. 1991.
- Weaver WD, Hill D, Fahrenbruch CE, et al. Use of the automatic external defibrillator in the management of out-of-hospital cardiac arrest. *N Engl J Med* 1988;319:661-666.
- Stults KR, Brown DD, Schug VL, Bean JA. Prehospital defibrillation performed by emergency medical technicians in rural communities. *N Engl J Med* 1984;310:219-223.
- Kerejakes DJ, Weaver WD, Anderson JL, et al. Time delays in the diagnosis and treatment of acute myocardial infarction: a tale of eight cities. Report from the Pre-hospital Study Group and the Cincinnati Heart Project. *Am Heart J* 1990;120:773-780.
- Weaver WD, Litwin PE, Martin JS, et al. Effect of age on use of thrombolytic therapy and mortality in acute myocardial infarction: the MITI Project Group. *J Am Coll Cardiol* 1991;18:657-662.
- Karagounis L, Ipsen SK, Jessop MR, et al. Impact of field-transmitted electrocardiography on time to in-hospital thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1990;66:786-791.
- Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-322.
- Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397-402.
- ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-360.
- Gersh BJ, Anderson JL. Thrombolysis and myocardial salvage: results of clinical trials and the animal paradigm—paradoxical or predictable? *Circulation* 1993;88:296-306.
- Castaigne AD, Herve C, Duval-Moulin AM, et al. Prehospital use of APSAC: results of a placebo-controlled study. *Am J Cardiol* 1989;64(suppl 2):30A-33A.
- Schofer J, Buttner J, Geng G, et al. Prehospital thrombolysis in acute myocardial infarction. *Am J Cardiol* 1990;66:1429-1433.
- GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian Region Early Anistreplase Trial. *BMJ* 1992;305:548-553.
- The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993;329:383-389.
- Adams J, Trent R, Rawles J. Earliest electrocardiographic evidence of myocardial infarction: implications for thrombolytic treatment. The GREAT Group. *BMJ* 1993;307:409-413.
- Gibler WB, Kerejakes DJ, Dean EN, et al. Prehospital diagnosis and treatment of acute myocardial infarction: a North-South perspective. The Cincinnati Heart Project and the Nashville Prehospital TPA trial. *Am Heart J* 1991;121:1-11.
- Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction: results from the Myocardial Infarction Triage and Intervention Registry. *Arch Intern Med* 1992;152:972-976.
- Rude RE, Poole WK, Muller JE, et al. Electrocardiographic and clinical criteria for recognition of acute myocardial infarction based on analysis of 3697 patients. *Am J Cardiol* 1983;52:936-942.
- Mauri F, Gasparini M, Barbonaglia L, et al. Prognostic significance of the extent of myocardial injury in acute myocardial infarction treated by streptokinase (the GISSI trial). *Am J Cardiol* 1989;63:1291-1295.
- Fuchs R, Scheidt S. Improved criteria for admission to cardiac care units. *JAMA* 1985;246:2037-2041.
- Nattel S, Warnica J, Ogilvie R. Indications for admission to a coronary care unit in patients with unstable angina. *Can Med Assoc J* 1980;122: 180-184.
- Eisenberg J, Horowitz L, Busch R, et al. Diagnosis of acute myocardial infarction in the ER: a prospective assessment of clinical decision making and the usefulness of immediate cardiac enzyme determination. *J Community Health* 1979;4:190-198.
- Seager S. Cardiac enzymes in the evaluation of chest pain. *Ann Emerg Med* 1980;9:346-349.
- Horowitz R, Morganroth J. Immediate detection of early high-risk patients with an acute myocardial infarction using two-dimensional echocardiographic evaluation of left ventricular regional wall abnormalities. *Am Heart J* 1982;103:814-822.

45. Wackers F, Kie K, Liem K, et al. Potential value of thallium-201 scintigraphy as a means of selecting patients for the coronary care unit. *Br Heart J.* 1979;41:111-117.
46. Pozen M, D'Agostino R, Selker H, et al. A predictive instrument to improve coronary-care-unit admission practices in acute ischemic heart disease. *N Engl J Med.* 1984;310:1273-1278.
47. Goldman L, Cook E, Brand D, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. *N Engl J Med.* 1988;318:797-803.
48. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. *Circulation.* 1994;90:583-612.
49. Kannel W. Prevalence and clinical aspects of unrecognized myocardial infarction and sudden unexpected death. *Circulation.* 1987;75(suppl II):II-4-II-5.
50. Grimm R, Tillingshast S, Daniels K, et al. Unrecognized myocardial infarction: experience in the multiple risk factor intervention trial (MRFIT). *Circulation.* 1987;75(suppl II):II-6-II-8.
51. Hedges JR, Young GP, Henkel GF, et al. Serial ECGs are less accurate than serial CK-MB results for emergency department diagnosis of myocardial infarction. *Ann Emerg Med.* 1992;21:1445-1450.
52. Gibler WB, Young GP, Hedges JR, et al. Acute myocardial infarction in chest pain patients with nondiagnostic ECGs: serial CK-MB sampling in the emergency department. The Emergency Medicine Cardiac Research Group. *Ann Emerg Med.* 1992;21:504-512.
53. Goldberg R, Gore J, Alpert J, et al. Incidence and case fatality rates of acute myocardial infarction (1975-1984): the Worcester Heart Attack Study. *Am Heart J.* 1988;115:761-767.
54. Gibler W, Lewis L, Erb R, et al. Early detection of acute myocardial infarction in patients presenting with chest pain and nondiagnostic ECGs: serial CKMB sampling in the emergency department. *Ann Emerg Med.* 1990;19:1359-1366.
55. Ellis AK. Serum protein measurements and the diagnosis of acute myocardial infarction. *Circulation.* 1991;83:1107-1109.
56. Adams J, Abendschein D, Jaffe A. Biochemical markers of myocardial injury: is MB creatine kinase the choice for the 1990s? *Circulation.* 1993;88:750-763.
57. Roberts R, Kleinman N. Earlier diagnosis and treatment of acute myocardial infarction necessitates the need for a "new diagnostic mind-set." *Circulation.* 1994;89:872-881.
58. Mair J, Dienstl F, Puschendorf B. Cardiac troponin T in the diagnosis of myocardial injury. *Crit Rev Clin Lab Sci.* 1992;29:31-57.
59. Puleo PR, Meyer D, Wathen C, et al. Use of a rapid assay of subforms of creatine kinase MB to diagnose or rule out acute myocardial infarction. *N Engl J Med.* 1994;331:561-566.
60. Mair J, Artner-Dworzak E, Lechleitner P, et al. Cardiac troponin T in diagnosis of acute myocardial infarction. *Clin Chem.* 1991;37:845-852.
61. Antman EM, Grudien C, Sacks D. Evaluation of a rapid bedside assay for detection of serum cardiac troponin T. *JAMA.* 1995;273:1279-1282.
62. Ohman EM, Armstrong P, Califf RM, et al. GUSTO IIa investigators: risk stratification in acute ischemic syndromes using serum troponin T. *J Am Coll Cardiol.* February 1995;25(special issue):148A. Abstract.
63. Rakilde J, Nissen H, Horder M, Thygesen K. Independent prognostic value of serum creatine kinase isoenzyme MB mass, cardiac troponin T and myosin light chain levels in suspected acute myocardial infarction: analysis of 28 months of follow-up in 196 patients. *J Am Coll Cardiol.* 1995;25:574-581.
64. Ohman EM, Casey C, Bengtson JR, Pryor D, Tormey W, Horgan JH. Early detection of acute myocardial infarction: additional diagnostic information from serum concentrations of myoglobin in patients without ST elevation. *Br Heart J.* 1990;63:335-338.
65. Zabel M, Hohnloser SH, Koster W, Prinz M, Kasper W, Just H. Analysis of creatine kinase, CK-MB, myoglobin, and troponin T time-activity curves for early assessment of coronary artery reperfusion after intravenous thrombolysis. *Circulation.* 1993;87:1542-1550.
66. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation.* 1975;52:360-368.
67. Madias JE, Hood WB Jr. Reduction of precordial ST-segment elevation in patients with anterior myocardial infarction by oxygen breathing. *Circulation.* 1976;53(suppl I):I-198-I-200.
68. Fillmore SJ, Shapiro M, Killip T. Arterial oxygen tension in acute myocardial infarction: serial analysis of clinical state and blood gas changes. *Am Heart J.* 1970;79:620-629.
69. Aubier M, Trippenbach T, Roussos C. Respiratory muscle fatigue during cardiogenic shock. *J Appl Physiol.* 1981;51:499-508.
70. Hyzy R, Popovich J. Mechanical ventilation and weaning. In: Carlson RW, Geheb MA, eds. *Principles and Practice of Medical Intensive Care.* Philadelphia, Pa: WB Saunders Co Ltd; 1993:924-943.
71. Friedberg CK. Acute coronary occlusion and myocardial infarction. In: Friedberg CK, ed. *Disease of the Heart.* 3rd ed. Philadelphia, Pa: WB Saunders Co Ltd; 1966:913-914.
72. Come PC, Pitt B. Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. *Circulation.* 1976;54:624-628.
73. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med.* 1994;330:1211-1217.
74. Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: a meta-analysis. *J Am Coll Cardiol.* 1992;19:671-677.
75. Das G, Talmers FN, Weissler AM. New observations on the effects of atropine on the sinoatrial and atrioventricular nodes in man. *Am J Cardiol.* 1975;36:281-285.
76. Pantridge JF, Webb SW, Adey AA, Geddes JS. The first hour after onset of acute myocardial infarction. In: Yu PN, Goodwin JF, eds. *Progress in Cardiology.* Philadelphia, Pa: Lea & Febiger; 1974:173-188.
77. Scheinman MM, Thorburn D, Abbott JA. Use of atropine in patients with acute myocardial infarction and sinus bradycardia. *Circulation.* 1975;52:627-633.
78. Kottmeier CA, Gravenstein JS. The parasympathomimetic activity of atropine and atropine methylbromide. *Anesthesiology.* 1968;29:1125-1133.
79. Massumi RA, Mason DT, Amsterdam EA, et al. Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardias. *N Engl J Med.* 1972;287:336-338.
80. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med.* 1980;303:897-902.
81. de Feyter PJ, van den Brand M, Serruys PW, Wijns W. Early angiography after myocardial infarction: what have we learned? *Am Heart J.* 1985;109:194-199.
82. DeWood MA, Stifter WF, Simpson CS, et al. Coronary arteriographic findings soon after non-Q-wave myocardial infarction. *N Engl J Med.* 1986;315:417-423.
83. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest: results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. *Circulation.* 1993;87:38-52.
84. Rogers WJ, Bowby LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993): observations from the National Registry of Myocardial Infarction. *Circulation.* 1994;90:2103-2114.
85. Villanueva FS, Sabia PJ, Afrookteh A, Pollock SG, Hwang LJ, Kaul S. Value and limitations of current methods of evaluating patients presenting to the emergency room with cardiac-related symptoms for determining long-term prognosis. *Am J Cardiol.* 1992;69:746-750.
86. Sabia P, Abbott RD, Afrookteh A, Keller MW, Touchstone DA, Kaul S. Importance of two-dimensional echocardiographic assessment of left ventricular systolic function in patients presenting to the emergency room with cardiac-related symptoms. *Circulation.* 1991;84:1615-1624.
87. Sabia P, Afrookteh A, Touchstone DA, Keller MW, Esquivel L, Kaul S. Value of regional wall motion abnormality in the emergency room diagnosis of acute myocardial infarction: a prospective study using two-dimensional echocardiography. *Circulation.* 1991;84(suppl I):I-85-I-92.
88. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Bierman FZ, Beller GA, Davidson TW, Davis JL, Douglas PS, Gillam LD, Lewis RP, Pearlman AS, Philbrick JT, Shah PM, Williams RG. ACC/AHA guidelines for clinical application of echocardiography. *Circulation.* In press.
89. Hilton TC, Thompson RC, Williams HJ, Salors R, Fulmer H, Stowers SA. Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol.* 1994;23:1016-1022.
90. Varetto T, Cantalupi D, Altieri A, Orlandi C. Emergency room technetium-99m sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiograms. *J Am Coll Cardiol.* 1993;22:1804-1808.

90. Honan MB, Harrell FE, Reimer KA, et al. Cardiac rupture, mortality and the timing of thrombolytic therapy: a meta-analysis. *J Am Coll Cardiol*. 1990;16:359-367.
91. Becker RC, Charlesworth A, Wilcox RG, et al. Cardiac rupture associated with thrombolytic therapy: impact of time to treatment in the Late Assessment of Thrombolytic Efficacy (LATE) Study. *J Am Coll Cardiol*. 1995;25:1063-1068.
92. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation*. 1994;89:1545-1556.
93. Langer A, Goodman SG, Topol EJ, et al, for the LATE Study Investigators. Late Assessment of Thrombolytic Efficacy (LATE) Study: prognosis in patients with non-Q wave myocardial infarction. *J Am Coll Cardiol*. 1996;27:1327-1332.
94. Braunwald E, Cannon CP. Non-Q wave and ST segment depression myocardial infarction: is there a role for thrombolytic therapy? *J Am Coll Cardiol*. 1996;27:1333-1334.
95. Van de Werf F. Thrombolysis for acute myocardial infarction: why is there no extra benefit after hospital discharge? *Circulation*. 1995;91:2862-2864.
96. Martin GV, Kennedy JW. Choice of thrombolytic agent. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction*. London, England: WB Saunders Co Ltd; 1994:71-105.
97. Antman EM. General hospital management. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction*. London, England: WB Saunders Co Ltd; 1994:42-44.
98. Christian TF, Gibbons RJ, Clements IP, Berger PB, Sylvester RH, Wagner GS. Prediction of myocardium at risk and collateral flow in acute myocardial infarction using electrocardiographic indices with comparison to radionuclide and angiographic measures. *J Am Coll Cardiol*. 1995;26:388-393.
99. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet*. 1993;342:759-766.
100. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet*. 1993;342:767-772.
101. Maggioni AP, Maseri A, Fresco C, et al. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis: the Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2). *N Engl J Med*. 1993;329:1442-1448.
102. Hillis LD, Forman S, Braunwald E. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction: the Thrombolysis in Myocardial Infarction (TIMI) Phase II co-Investigators. *J Am Coll Cardiol*. 1990;16:313-315.
103. Kleiman NS, White HD, Ohman EM, et al. Mortality within 24 hours of thrombolysis for myocardial infarction: the importance of early reperfusion. The GUSTO Investigators, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *Circulation*. 1994;90:2658-2665.
104. Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial hemorrhage during thrombolytic therapy. *Lancet*. 1993;342:1523-1528.
105. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med*. 1995;332:1418-1424.
106. De Jaegere PP, Arnold AA, Balk AH, Simoons ML. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. *J Am Coll Cardiol*. 1992;19:289-294.
107. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) phase II trial. *N Engl J Med*. 1989;320:618-627.
108. National Heart Attack Alert Program Coordinating Committee, 60 Minutes to Treatment Working Group. Emergency department: rapid identification and treatment of patients with acute myocardial infarction. *Ann Emerg Med*. 1994;23:311-329.
109. Fendrick AM, Ridker PM, Bloom BS. Improved health benefits of increased use of thrombolytic therapy. *Arch Intern Med*. 1994;154:1605-1609.
110. Ryan TJ, Bauman WB, Kennedy JW, et al. ACC/AHA guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). *J Am Coll Cardiol*. 1993;22:2033-2054.
111. Meyer J, Merx W, Schmitz H, et al. Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. *Circulation*. 1982;66:905-913.
112. Meier B. Balloon angioplasty for acute myocardial infarction: was it buried alive? *Circulation*. 1990;82:2243-2245.
113. Brundage BH. Because we can, should we? *J Am Coll Cardiol*. 1990;15:544-545.
114. O'Keefe JH, Rutherford BD, McConahay DR, et al. Early and late results of coronary angioplasty without antecedent thrombolytic therapy for acute myocardial infarction. *Am J Cardiol*. 1989;64:1221-1230.
115. O'Keefe JH, Rutherford BD, McConahay DR, et al. Myocardial salvage with direct coronary angioplasty for acute infarction. *Am Heart J*. 1992;123:1-6.
116. Stone GW, Rutherford BD, McConahay DR, et al. Direct coronary angioplasty in acute myocardial infarction: outcome in patients with single vessel disease. *J Am Coll Cardiol*. 1990;15:534-543.
117. Kander NH, O'Neill W, Topol EJ, Gallois L, Mileski R, Ellis SG. Long-term follow-up of patients treated with coronary angioplasty for acute myocardial infarction. *Am Heart J*. 1989;118:228-233.
118. Zijlstra F, de Boer MJ, Hoornje JC, Reijers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med*. 1993;328:680-684.
119. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfensperger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction: the Mayo Coronary Care Unit and Catheterization Laboratory Groups. *N Engl J Med*. 1993;328:685-691.
120. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med*. 1993;328:673-679.
121. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. *Circulation*. 1995;91:476-485.
122. Cannon CP, Henry TD, Schweiger MJ, et al. TIMI 9 Registry Investigators and Coordinators. Current management of ST elevation myocardial infarction and outcome of thrombolytic ineligible patients: results of the multi-center TIMI 9 registry. *J Am Coll Cardiol*. 1995;25:231A. Abstract.
123. Rogers WJ, Dean LS, Moore PB, et al. Comparison of primary angioplasty versus thrombolytic therapy for acute myocardial infarction. *Am J Cardiol*. 1994;74:111-118.
124. Tiefenbrunn AJ, Chandra NC, French WJ, Rogers WJ. Experience with primary PTCA compared to alteplase in patients with acute myocardial infarction. *Circulation*. 1995;92(suppl 1):I-138. Abstract.
125. Every N, Weaver WD, Parsons L, Martin JS, for the MITI Project Investigators. Direct PTCA vs thrombolysis: immediate and one year outcome and procedure utilization for the two treatment strategies. *Circulation*. 1995;92(suppl 1):I-138. Abstract.
126. Cannon CP, Braunwald E. Time to reperfusion: the critical modulator in thrombolytic and primary angioplasty. *J Thrombosis Thrombolysis* 1996;3:109-117.
127. Ellis SG. GUSTO II: primary PTCA versus thrombolysis substudy. Presented at the American College of Cardiology Annual Scientific Session; March 1996: Orlando, Fla.
128. Kirklin JK, Akins CW, Blackstone EH, et al. Guidelines and indications for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Artery Bypass Graft Surgery). *J Am Coll Cardiol*. 1991;17:543-589.
129. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. *Circulation*. 1995;91:2335-2344.
130. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. *Circulation*. 1995;91:2325-2334.

131. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW. Coronary Artery Surgery Study. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. *J Am Coll Cardiol.* 1995;25:1000-1009.
132. Berg R Jr, Selinger SL, Leonard JJ, Grunwald RP, O'Grady WP. Immediate coronary artery bypass for acute evolving myocardial infarction. *J Thorac Cardiovasc Surg.* 1981;81:493-497.
133. DeWood MA, Spores J, Notske RN, et al. Medical and surgical management of myocardial infarction. *Am J Cardiol.* 1979;44:1356-1364.
134. Phillips SJ, Zeff RH, Skinner JR, Toon RS, Grignon A, Kongthaworn C. Reperfusion protocol and results in 738 patients with evolving myocardial infarction. *Ann Thorac Surg.* 1986;41:119-125.
135. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. *J Am Coll Cardiol.* 1987;10:756-760.
136. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). *N Engl J Med.* 1992;326:242-250, 310-318.
137. Willerson JT, Campbell WB, Winniford MD, et al. Conversion from chronic to acute coronary artery disease: speculation regarding mechanisms. *Am J Cardiol.* 1984;54:1349-1354.
138. Ambrose JA, Hjemdahl-Monsen CE, Borrico S, Gorlin R, Fuster V. Angiographic demonstration of a common link between unstable angina pectoris and non-Q-wave acute myocardial infarction. *Am J Cardiol.* 1988;61:244-247.
139. Hussain KM, Gould L, Bharathan T, Angirekula M, Choubey S, Karpov Y. Arteriographic morphology and intracoronary thrombus in patients with unstable angina, non-Q wave myocardial infarction and stable angina pectoris. *Angiology.* 1995;46:181-189.
140. Keen WD, Savage MP, Fischman DL, et al. Comparison of coronary angiographic findings during the first six hours of non-Q-wave and Q-wave myocardial infarction. *Am J Cardiol.* 1994;74:324-328.
141. Dacanay S, Kennedy HL, Uretz E, Parrillo JE, Klein LW. Morphological and quantitative angiographic analyses of progression of coronary stenoses: a comparison of Q-wave and non-Q-wave myocardial infarction. *Circulation.* 1994;90:1739-1746.
142. Surawicz B, Uhley H, Borun R, et al. The quest for optimal electrocardiography: Task Force I. Standardization of terminology and interpretation. *Am J Cardiol.* 1978;41:130-145.
143. Gibson RS. Non-Q wave myocardial infarction. In: Gersh BJ, Rahimtoola SH, eds. *Acute Myocardial Infarction.* New York, NY: Elsevier Science; 1991:284-307.
144. Pierard LA. Non-Q wave, incomplete infarction. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction.* London, England: WB Saunders Co Ltd; 1994:315-330.
145. Cannon DS, Levy W, Cohen LS. The short- and long-term prognosis of patients with transmural and nontransmural myocardial infarction. *Am J Med.* 1976;61:452-458.
146. Szkelo M, Goldberg R, Kennedy HL, Tonascia JA. Survival of patients with nontransmural myocardial infarction: a population-based study. *Am J Cardiol.* 1978;42:648-652.
147. Fabricius-Bjerre N, Munkvad M, Knudsen JB. Subendocardial and transmural myocardial infarction: a five year survival study. *Am J Med.* 1979;66: 986-990.
148. Thanavaro S, Krone RJ, Kleiger RE, et al. In-hospital prognosis of patients with first nontransmural and transmural infarctions. *Circulation.* 1980;61: 29-33.
149. Kudenchuk PJ, Ho MT, Weaver WD, et al. Accuracy of computer-interpreted electrocardiography in selecting patients for thrombolytic therapy: MITI Project Investigators. *J Am Coll Cardiol.* 1991;17:1486-1491.
150. Karlsson JE, Berglund U, Bjorkholm A, Ohlsson J, Swahn E, Wallentin L, TRIC Study Group. Thrombolysis with recombinant human tissue-type plasminogen activator during instability in coronary artery disease: effect on myocardial ischemia and need for coronary revascularization. *Am Heart J.* 1992;124:1419-1426.
151. Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. *Ann Intern Med.* 1991;115:173-177.
152. Rothbaum DA, Linnemeier TJ, Landin RJ, et al. Emergency percutaneous transluminal coronary angioplasty in acute myocardial infarction: a 3 year experience. *J Am Coll Cardiol.* 1987;10:264-272.
153. Kulick DL, Rahimtoola SH. Risk stratification in survivors of acute myocardial infarction: routine cardiac catheterization and angiography is a reasonable approach in most patients. *Am Heart J.* 1991;121:641-656.
154. Antman EM, Tanasijevic MJ, Cannon CP, et al. Prediction of risk by cardiac-specific troponin I in patients with acute coronary syndromes. *N Engl J Med.* 1996;335(18):1342-1349.
155. Drew BJ, Ide B, Sparacino PS. Accuracy of bedside electrocardiographic monitoring: a report on current practices of critical care nurses. *Heart Lung.* 1991;20:597-607.
156. Romhilt DW, Bloomfield SS, Chou TC, Fowler NO. Unreliability of conventional electrocardiographic monitoring for arrhythmia detection in coronary care units. *Am J Cardiol.* 1973;31:457-461.
157. Vatner SF, McRitchie RJ, Maroko PR, Patrick TA, Braunwald E. Effects of catecholamines, exercise, and nitroglycerin on the normal and ischemic myocardium in conscious dogs. *J Clin Invest.* 1974;54:563-575.
158. Chobanian AV, Lille RD, Tercyak A, Blevins P. The metabolic and hemodynamic effects of prolonged bed rest in normal subjects. *Circulation.* 1974;49:551-559.
159. Winslow EH. Cardiovascular consequences of bed rest. *Heart Lung.* 1985; 14:236-246.
160. Riegel B, Thomason T, Carlson B, Gocia I. Are nurses still practicing coronary precautions? A national survey of nursing care of acute myocardial infarction patients. *Am J Crit Care.* 1996;5:91-98.
161. Metzger BL, Therrien B. Effect of position on cardiovascular response during the Valsalva maneuver. *Nurs Res.* 1990;39:198-202.
162. Taggart P, Sutton P, John R, Lab M, Swanton H. Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre. *Br Heart J.* 1992;67:221-229.
163. Folta A, Metzger BL, Therrien B. Preexisting physical activity level and cardiovascular responses across the Valsalva maneuver. *Nurs Res.* 1989;38: 139-143.
164. Porth CJ, Bamrah VS, Tristani FE, Smith JJ. The Valsalva maneuver: mechanisms and clinical implications. *Heart Lung.* 1984;13:507-518.
165. Storm DS, Metzger BL, Therrien B. Effects of age on autonomic cardiovascular responsiveness in healthy men and women. *Nurs Res.* 1989;38:326-330.
166. Goldstein IB, Shapiro D, Hui KK, Yu JL. Blood pressure response to the second cup of coffee. *Psychosom Med.* 1990;52:337-345.
167. Astrup A, Toumbro S, Cannon S, Hein P, Breum L, Madsen J. Dose-dependent effect on serum cholesterol and apoprotein B concentrations by consumption of boiled, non-filtered coffee. *Atherosclerosis.* 1990;83:257-261.
168. Myers MG, Harris L, Leenen FH, Grant DM. Caffeine as a possible cause of ventricular arrhythmias during the healing phase of acute myocardial infarction. *Am J Cardiol.* 1987;59:1024-1028.
169. Pincomb GA, Lovallo WR, Passey RB, Whitsett TL, Silverstein SM, Wilson MF. Effects of caffeine on vascular resistance, cardiac output and myocardial contractility in young men. *Am J Cardiol.* 1985;56:119-122.
170. Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ. Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. *Drug Alcohol Depend.* 1993;32:239-246.
171. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *BMJ.* 1990;300:1558-1559.
172. Hofer I, Battig K. Cardiovascular, behavioral, and subjective effects of caffeine under field conditions. *Pharmacol Biochem Behav.* 1994;48:899-908.
173. Lynn LA, Kissinger JF. Coronary precautions: should caffeine be restricted in patients after myocardial infarction? *Heart Lung.* 1992;21:365-371.
174. Pasqualucci V. Advances in the management of cardiac pain. In: Benedett C, ed. *Advances in Pain Research and Therapy.* New York, NY: Raven Press; 1984:501-519.
175. Herlitz J. Analgesia in myocardial infarction. *Drugs.* 1989;37:939-944.
176. Fletcher V. An individualized teaching programme following primary uncomplicated myocardial infarction. *J Adv Nurs.* 1987;12:195-200.
177. Macland JG, Havik OE. The effects of an in-hospital educational programme for myocardial infarction patients. *Scand J Rehabil Med.* 1987;19: 57-65.
178. Duryee R. The efficacy of inpatient education after myocardial infarction. *Heart Lung.* 1992;21:217-225.
179. Mazzuca SA. Does patient education in chronic disease have therapeutic value? *J Chronic Dis.* 1982;35:521-529.

180. Johnson JE, Christman NJ, Stitt C. Personal control interventions: short- and long-term effects on surgical patients. *Res Nurs Health.* 1985;8:131-145.
181. Lindeman CA. Patient education. *Annu Rev Nurs Res.* 1988;6:29-60.
182. Edwardson SR. Outcomes of coronary care in the acute care setting. *Res Nurs Health.* 1988;11:215-222.
183. Lindsay C, Jennrich JA, Biemolt M. Programmed instruction booklet for cardiac rehabilitation teaching. *Heart Lung.* 1991;20:648-653.
184. Thompson DR, Meddis R. A prospective evaluation of in-hospital counselling for first time myocardial infarction men. *J Psychosom Res.* 1990;34: 237-248.
185. Goldstein S, Bayes-de-Luna A, Soldevila JG. *Sudden Cardiac Death.* Armonk, NY: Futura Publishing Co Inc; 1994.
186. Dracup K, Moser DK, Guzy PM, Taylor SE, Marsden C. Is cardiopulmonary resuscitation training deleterious for family members of cardiac patients? *Am J Public Health.* 1994;84:116-118.
187. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med.* 1993; 119:1187-1197.
188. Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction.* 1994;89: 1461-1470.
189. Dixon RA, Edwards IR, Pilcher J. Diazepam in immediate post-myocardial infarct period: a double blind trial. *Br Heart J.* 1980;43:535-540.
190. Simpson T, Shaver J. Cardiovascular responses to family visits in coronary care unit patients. *Heart Lung.* 1990;19:344-351.
191. Schulte DA, Burrell LO, Gueldner SH, et al. Pilot study of the relationship between heart rate and ectopy and unrestricted vs restricted visiting hours in the coronary care unit. *Am J Crit Care.* 1993;2:134-136.
192. Guidelines for advanced life support: a statement by the Advanced Life Support Working Party of the European Resuscitation Council. 1992. *Resuscitation.* 1992;24:111-121.
193. Collinson PO, Ramhamadamy EM, Stubbs PJ, et al. Rapid enzyme diagnosis of patients with acute chest pain reduces patient stay in the coronary care unit. *Ann Clin Biochem.* 1993;30:17-22.
194. Hopkins LE, Crabbe SJ, Chase SL. Use of a proprietary database to examine lengths of hospital stay of patients who received drug therapy for acute myocardial infarction. *Am J Hosp Pharm.* 1989;46:957-961.
195. Topol EJ, Burek K, O'Neill WW, et al. A randomized controlled trial of hospital discharge three days after myocardial infarction in the era of reperfusion. *N Engl J Med.* 1988;318:1083-1088.
196. Mark DB, Sigmon K, Topol EJ, et al. Identification of acute myocardial infarction patients suitable for early hospital discharge after aggressive interventional therapy: results from the Thrombolysis and Angioplasty in Acute Myocardial Infarction Registry. *Circulation.* 1991;83:1186-1193.
197. Newby LK, Califf RM, Guerci A, et al. Early discharge in the thrombolytic era: an analysis of criteria for uncomplicated infarction from the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial. *J Am Coll Cardiol.* 1996;27:625-632.
198. Normand SL, Glickman ME, Sharma RG, McNeil BJ. Using admission characteristics to predict short-term mortality from myocardial infarction in elderly patients: results from the Cooperative Cardiovascular Project. *JAMA.* 1996;275:1322-1328.
199. Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41 021 patients. *Circulation.* 1995;91:1659-1668.
200. Gheorghiade M, Anderson J, Rosman H, et al. Risk identification at the time of admission to coronary care unit in patients with suspected myocardial infarction. *Am Heart J.* 1988;116:1212-1217.
201. Pozen MW, Stechmiller JK, Voigt GC. Prognostic efficacy of early clinical categorization of myocardial infarction patients. *Circulation.* 1977;56:816-819.
202. Krone RJ. The role of risk stratification in the early management of a myocardial infarction. *Ann Intern Med.* 1992;116:223-237.
203. Kloner RA, Parisi AF. Acute myocardial infarction: diagnostic and prognostic applications of two-dimensional echocardiography. *Circulation.* 1987; 75:521-524.
204. Parsons RW, Jamrozik KD, Hobbs MS, Thompson PL. Early identification of patients at low risk of death after myocardial infarction and potentially suitable for early hospital discharge. *BMJ.* 1994;308:1006-1010.
205. Ayanian JZ, Hauptman PJ, Guadagnoli E, Antman EM, Pashos CL, McNeil BJ. Knowledge and practices of generalist and specialist physicians regarding drug therapy for acute myocardial infarction. *N Engl J Med.* 1994;331:1136-1142.
206. Van der Werf F, Topol EJ, Kerry KL, et al. Variations in patient management and outcomes for acute myocardial infarction in the United States and other countries: results from the GUSTO trial. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *JAMA.* 1995;273:1586-1591.
207. Pilote L, Califf RM, Sapp S, et al. Regional variation across the United States in the management of acute myocardial infarction: GUSTO-1 Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *N Engl J Med.* 1995;333: 565-572.
208. Peterson ED, Wright SM, Daley J, Thibault GE. Racial variation in cardiac procedure use and survival following acute myocardial infarction in the Department of Veterans Affairs. *JAMA.* 1994;271:1175-1180.
209. Pashos CL, Newhouse JP, McNeil BJ. Temporal changes in the care and outcomes of elderly patients with acute myocardial infarction, 1987 through 1990. *JAMA.* 1993;270:1832-1836.
210. Iaken LH, Smith HL, Lake ET. Lower Medicare mortality among a set of hospitals known for good nursing care. *Medical Care.* 1994;32:771-787.
211. Tosler GH, Muller JE, Stone PH, et al. Pericarditis in acute myocardial infarction: characterization and clinical significance. *Am Heart J.* 1989;117: 86-92.
212. Oliva PB, Hammill SC, Talano JV. Effect of definition on incidence of postinfarction pericarditis: is it time to redefine postinfarction pericarditis? *Circulation.* 1994;90:1537-1541.
213. Wall TC, Califf RM, Harrelson-Woodlief L, et al. Usefulness of a pericardial friction rub after thrombolytic therapy during acute myocardial infarction in predicting amount of myocardial damage: the TAMI Study Group. *Am J Cardiol.* 1990;66:1418-1421.
214. Oliva PB, Hammill SC. The clinical distinction between regional postinfarction pericarditis and other causes of postinfarction chest pain: ancillary observations regarding the effect of lytic therapy upon the frequency of postinfarction pericarditis, postinfarction angina, and reinfarction. *Clin Cardiol.* 1994;17:471-478.
215. Oliva PB, Hammill SC, Talano JV. T wave changes consistent with epicardial involvement in acute myocardial infarction: observations in patients with a postinfarction pericardial effusion without clinically recognized postinfarction pericarditis. *J Am Coll Cardiol.* 1994;24:1073-1077.
216. Widimsky P, Gregor P. Recent atrial fibrillation in acute myocardial infarction: a sign of pericarditis. *Cor Vasa.* 1993;35:230-232.
217. Erhardt LR. Clinical and pathological observations in different types of acute myocardial infarction. *Acta Med Scand.* 1974;560(suppl):1-78.
218. Spodick D. Pericardial complications of myocardial infarction. In: Francis GS, Alpert JS, eds. *Modern Coronary Care.* Boston, Mass: Little Brown and Co; 1990:331-339.
219. Shahar A, Hod H, Barabash GM, Kaplinsky E, Motro M. Disappearance of a syndrome: Dressler's syndrome in the era of thrombolysis. *Cardiology.* 1994;85:255-258.
220. Berman J, Haffajee CI, Alpert JS. Therapy of symptomatic pericarditis after myocardial infarction: retrospective and prospective studies of aspirin, indomethacin, prednisone, and spontaneous resolution. *Am Heart J.* 1981; 101:750-753.
221. Lilavie CJ, Gersh PJ. Mechanical and electrical complication of acute myocardial infarction. *Mayo Clin Proc.* 1990;65:709-730.
222. Friedman PL, Brown EJ Jr, Gunther S, et al. Coronary vasoconstrictor effect of indomethacin in patients with coronary-artery disease. *N Engl J Med.* 1981;305:1171-1175.
223. Hammerman H, Schoen FJ, Braunwald E, Kloner RA. Drug-induced expansion of infarct: morphologic and functional correlations. *Circulation.* 1984;69:611-617.
224. Bulkley BH, Roberts WC. Steroid therapy during acute myocardial infarction: a cause of delayed healing and of ventricular aneurysm. *Am J Med.* 1974;56:244-250.
225. Kloner RA, Fishbein MC, Lew H, Maroko PR, Braunwald E. Mummification of the infarcted myocardium by high dose corticosteroids. *Circulation.* 1978;57:56-63.
226. Schaer DH, Liebhoff RH, Katz RJ, et al. Recurrent early ischemic events after thrombolysis for acute myocardial infarction. *Am J Cardiol.* 1987;59: 788-792.
227. Weisman HF, Healy B. Myocardial infarct expansion, infarct extension, and

- reinfarction: pathophysiologic concepts. *Prog Cardiovasc Dis.* 1987;30:73-110.
228. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-682.
229. Hutchins GM, Bulkley BH. Infarct expansion versus extension: two different complications of acute myocardial infarction. *Am J Cardiol.* 1978;41:1127-1132.
230. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease: I. treatments following myocardial infarction. *JAMA.* 1988;260:2088-2093.
231. Ohman EM, Calif RM, Topol EJ, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction: the TAMI Study Group. *Circulation.* 1990;82:781-791.
232. Nakamura F, Minamino T, Higashino Y, et al. Cardiac free wall rupture in acute myocardial infarction: ameliorative effect of coronary reperfusion. *Clin Cardiol.* 1992;15:244-250.
233. Pollak H, Nobis H, Mlczech J. Frequency of left ventricular free wall rupture complicating acute myocardial infarction since the advent of thrombolysis. *Am J Cardiol.* 1994;74:184-186.
234. Becker RC, Gore JM, Lambrew C, et al. A composite view of cardiac rupture in the United States National Registry of Myocardial Infarction. *J Am Coll Cardiol.* 1996;27:1321-1326.
235. Nunez L, de la Llana R, Lopez Sendon J, Coma I, Gil Aguado M, Larrea JL. Diagnosis and treatment of subacute free wall ventricular rupture after infarction. *Ann Thorac Surg.* 1983;35:525-529.
236. Balakumaran K, Verbaan CJ, Essed CE, et al. Ventricular free wall rupture: sudden, subacute, slow, sealed and stabilized varieties. *Eur Heart J.* 1984;5:282-288.
237. Calif RM, Topol EJ, George BS, et al. Characteristics and outcome of patients in whom reperfusion with intravenous tissue-type plasminogen activator fails: results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I Trial. *Circulation.* 1988;77:1090-1099.
238. Lee L, Bates ER, Pitt B, Walton JA, Laufer N, O'Neill WW. Percutaneous transluminal coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. *Circulation.* 1988;78:1345-1351.
239. Goldberg RJ, Gore JM, Alpert JS, et al. Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community-wide perspective, 1975 to 1988. *N Engl J Med.* 1991;325:1117-1122.
240. Bentgson JR, Kaplan AJ, Pieper KS, et al. Prognosis in cardiogenic shock after acute myocardial infarction in the interventional era. *J Am Coll Cardiol.* 1992;20:1482-1489.
241. Hochman JS, Boland J, Sleeper LA, et al. Current spectrum of cardiogenic shock and effect of early revascularization on mortality: results of an International Registry. SHOCK Registry Investigators. *Circulation.* 1995;91:873-881.
242. Allen BS, Rosenkranz E, Buckberg GD, et al. Studies on prolonged acute regional ischemia, VI: myocardial infarction with left ventricular power failure. A medical/surgical emergency requiring urgent revascularization with maximal protection of remote muscle. *J Thorac Cardiovasc Surg.* 1989;98:691-703.
243. Allen BS, Buckberg GD, Fontan FM, et al. Superiority of controlled surgical reperfusion versus percutaneous transluminal coronary angioplasty in acute coronary occlusion. *J Thorac Cardiovasc Surg.* 1993;105:864-884.
244. O'Connor GT, Plume SK, Olmstead EM, et al. Multivariate prediction of in-hospital mortality associated with coronary artery bypass graft surgery: Northern New England Cardiovascular Disease Study Group. *Circulation.* 1992;85:2110-2118.
245. Lemmer JH, Ferguson DW, Rakel BA, Rossi NP. Clinical outcome of emergency repeat coronary artery bypass surgery. *J Cardiovasc Surg (Torino).* 1990;31:492-497.
246. Zehender M, Kasper W, Kauder E, et al. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med.* 1993;328:981-988.
247. Berger PB, Ryan TJ. Inferior myocardial infarction: high-risk subgroups. *Circulation.* 1990;81:401-411.
248. Weinschel AJ, Isner JM, Salem DN, Konstam MS. The coronary anatomy of right ventricular infarction: relationship between the site of right coronary artery occlusion and origin of the right ventricular free wall branches. *Circulation.* 1983;68(suppl III):III-351. Abstract.
249. Andersen HR, Falk E, Nielsen D. Right ventricular infarction: frequency, size and topography in coronary heart disease: a prospective study comprising 107 consecutive autopsies from a coronary care unit. *J Am Coll Cardiol.* 1987;10:1223-1232.
250. Lee FA. Hemodynamics of the right ventricle in normal and diseased states. *Cardiol Clin.* 1992;10:59-67.
251. Cross CE. Right ventricular pressure and coronary flow. *Am J Physiol.* 1962;202:12-16.
252. Haupt HM, Hutchins GM, Moore GW. Right ventricular infarction: role of the moderator band artery in determining infarct size. *Circulation.* 1983;67:1268-1272.
253. Setaro JF, Cabin HS. Right ventricular infarction. *Cardiol Clin.* 1992;10:69-90.
254. Goldstein JA, Vlahakes GJ, Verrier ED, et al. The role of right ventricular systolic dysfunction and elevated intrapericardial pressure in the genesis of low output in experimental right ventricular infarction. *Circulation.* 1982;65:513-522.
255. Ferguson JJ, Diver DJ, Boldt M, Pasternak RC. Significance of nitroglycerin-induced hypotension with inferior wall acute myocardial infarction. *Am J Cardiol.* 1989;64:311-314.
256. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation.* 1990;82:359-368.
257. Goldstein JA, Tweddell JS, Barzilai B, Yagi Y, Jaffe AS, Cox JL. Importance of left ventricular function and systolic ventricular interaction to right ventricular performance during acute right heart ischemia. *J Am Coll Cardiol.* 1992;19:704-711.
258. Dell' Italia LJ, Starling MR, O'Rourke RA. Physical examination for exclusion of hemodynamically important right ventricular infarction. *Ann Intern Med.* 1983;99:608-611.
259. Dell' Italia LJ, Starling MR, Crawford MH, Boros BL, Chaudhuri TK, O'Rourke RA. Right ventricular infarction: identification by hemodynamic measurements before and after volume loading and correlation with noninvasive techniques. *J Am Coll Cardiol.* 1984;4:931-939.
260. Cohn JN, Guiha NH, Broder MI, Limas CJ. Right ventricular infarction: clinical and hemodynamic features. *Am J Cardiol.* 1974;33:209-214.
261. Robalino BD, Whitlow PL, Underwood DA, Salcedo EE. Electrocardiographic manifestations of right ventricular infarction. *Am Heart J.* 1989;118:138-144.
262. Braat SH, Brugada P, De Zwaan C, Coenegracht JM, Wellens HJ. Value of electrocardiogram in diagnosing right ventricular involvement in patients with an acute inferior wall myocardial infarction. *Br Heart J.* 1983;49:368-372.
263. Sharkey SW, Shelley W, Carlyle PF, Rysavy J, Cohn JN. M-mode and two-dimensional echocardiographic analysis of the septum in experimental right ventricular infarction: correlation with hemodynamic alterations. *Am Heart J.* 1985;110:1210-1218.
264. Lopez-Sendon J, Lopez de Sa E, Roldan I, Fernandez de Soria R, Ramos F, Martin Jdraque L. Inversion of the normal interatrial septum convexity in acute myocardial infarction: incidence, clinical relevance and prognostic significance. *J Am Coll Cardiol.* 1990;15:801-805.
265. Manno BV, Bemis CE, Carver J, Mintz GS. Right ventricular infarction complicated by right to left shunt. *J Am Coll Cardiol.* 1983;1:554-557.
266. Goldstein JA, Vlahakes GJ, Verrier ED, et al. Volume loading improves low cardiac output in experimental right ventricular infarction. *J Am Coll Cardiol.* 1983;2:270-278.
267. Dell' Italia LJ, Starling MR, Blumhardt R, Lasher JC, O'Rourke RA. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation.* 1985;72:1327-1335.
268. Braat SH, De Zwaan C, Brugada P, Coenegracht JM, Wellens HJ. Right ventricular involvement with acute inferior wall myocardial infarction identifies high risk of developing atrioventricular nodal conduction disturbances. *Am Heart J.* 1984;107:1183-1187.
269. Love JC, Hassjajee CI, Gore JM, Alpert JS. Reversibility of hypotension and shock by atrial or atrioventricular sequential pacing in patients with right ventricular infarction. *Am Heart J.* 1984;108:5-13.
270. Sugiura T, Iwasaka T, Takahashi N, et al. Atrial fibrillation in inferior wall Q-wave acute myocardial infarction. *Am J Cardiol.* 1991;67:1135-1136.
271. Fantidis P, Castejon R, Fernandez Ruiz A, Madero-Jarabo R, Cordovilla G, Sanz Galeote E. Does a critical hemodynamic situation develop from right ventriculotomy and free wall infarct or from small changes in

- dysfunctional right ventricle afterload? *J Cardiovasc Surg (Torino)*. 1992;33:229-234.
272. Braat SH, Ramentol M, Halders S, Wellens HJ. Reperfusion with streptokinase of an occluded right coronary artery: effects on early and late right and left ventricular ejection fraction. *Am Heart J*. 1987;113:257-260.
  273. Schuler G, Hofmann M, Schwarz F, et al. Effect of successful thrombolytic therapy on right ventricular function in acute inferior wall myocardial infarction. *Am J Cardiol*. 1984;54:951-957.
  274. Moreyra AE, Suh C, Porway MN, Kostis JB. Rapid hemodynamic improvement in right ventricular infarction after coronary angioplasty. *Chest*. 1988;94:197-199.
  275. Berger PB, Ruocco NA Jr, Ryan TJ, et al. Frequency and significance of right ventricular dysfunction during inferior wall left ventricular myocardial infarction treated with thrombolytic therapy (results from the thrombolysis in myocardial infarction [TIMI] II trial): the TIMI Research Group. *Am J Cardiol*. 1993;71:1148-1152.
  276. Polak JF, Holman BL, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. *J Am Coll Cardiol*. 1983;2:217-224.
  277. Lloyd EA, Gersh BJ, Kennelly BM. Hemodynamic spectrum of "dominant" right ventricular infarction in 19 patients. *Am J Cardiol*. 1981;48:1016-1022.
  278. Klein HO, Tordjman T, Ninio R, et al. The early recognition of right ventricular infarction: diagnostic accuracy of the electrocardiographic V<sub>2</sub>R lead. *Circulation*. 1983;67:558-565.
  279. Bellamy GR, Rasmussen HH, Nasser FN, Wiseman JC, Cooper RA. Value of two-dimensional echocardiography, electrocardiography, and clinical signs in detecting right ventricular infarction. *Am Heart J*. 1986;112:304-309.
  280. Hospital Infection Control Practices Advisory Committee (HICPAC) and the National Center for Infectious Diseases (NCID). CDC. Intravascular device-related infections: an overview (Part 1). Recommendations for prevention of intravascular device-related infections (Part 2). (PB96138102). *Federal Register*. 1995;49:995.
  281. Scheidt S, Wilner G, Mueller H, et al. Intra-aortic balloon counterpulsation in cardiogenic shock: report of a co-operative clinical trial. *N Engl J Med*. 1973;288:979-984.
  282. Leinbach RC, Gold HK, Harper RW, Buckley MJ, Austen WG. Early intraaortic balloon pumping for anterior myocardial infarction without shock. *Circulation*. 1978;58:204-210.
  283. Sammel NL, O'Rourke MF. Arterial counterpulsation in continuing myocardial ischaemia after acute myocardial infarction. *Br Heart J*. 1979;42:579-582.
  284. DeWood MA, Notske RN, Hensley GR, et al. Intraaortic balloon counterpulsation with and without reperfusion for myocardial infarction shock. *Circulation*. 1980;61:1105-1112.
  285. Cohn LH. Surgical management of acute and chronic cardiac mechanical complications due to myocardial infarction. *Am Heart J*. 1981;102:1049-1060.
  286. Levine FH, Gold HK, Leinbach RC, Daggett WM, Austen WG, Buckley MJ. Management of acute myocardial ischemia with intraaortic balloon pumping and coronary bypass surgery. *Circulation*. 1978;58(suppl I):I-69-I-72.
  287. Urschel CW, Eber L, Forrester J, Matloff J, Carpenter R, Sonnenblick E. Alteration of mechanical performance of the ventricle by intraaortic balloon counterpulsation. *Am J Cardiol*. 1970;25:546-551.
  288. Weber KT, Janicki JS. Intraaortic balloon counterpulsation: a review of physiologic principles, clinical results and device safety. *Ann Thorac Surg*. 1994;17:602-636.
  289. Powell WJ, Daggett WM, Magro AE, et al. Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption, and coronary blood flow in dogs. *Circ Res*. 1970;26:753-764.
  290. Williams DO, Korr KS, Gewirtz H, Most AS. The effect of intraaortic balloon counterpulsation on regional myocardial blood flow and oxygen consumption in the presence of coronary artery stenosis in patients with unstable angina. *Circulation*. 1982;66:593-597.
  291. Kern MJ, Aguirre FV, Tatineni S, et al. Enhanced coronary blood flow velocity during intraaortic balloon counterpulsation in critically ill patients. *J Am Coll Cardiol*. 1993;21:359-368.
  292. Lee L, Erbel R, Brown TM, Laufer N, Meyer J, O'Neill WW. Multicenter registry of angioplasty therapy of cardiogenic shock: initial and long-term survival. *J Am Coll Cardiol*. 1991;17:599-603.
  293. Flaherty JT, Becker LC, Weiss JL, et al. Results of a randomized prospective trial of intraaortic balloon counterpulsation and intravenous nitroglycerin in patients with acute myocardial infarction. *J Am Coll Cardiol*. 1985;6:434-446.
  294. Ohman EM, Calif RM, George BS, et al. The use of intraaortic balloon pumping as an adjunct to reperfusion therapy in acute myocardial infarction: the Thrombolytic and Angioplasty in Myocardial Infarction (TAMI) Study Group. *Am Heart J*. 1991;121:895-901.
  295. Ohman EM, George BS, White CJ, et al. the Randomized IABP Study Group. Use of aortic counterpulsation to improve sustained coronary artery patency during acute myocardial infarction: results of a randomized trial. *Circulation*. 1994;90:792-799.
  296. Griffin J, Grines CL, Marsalese D, et al. A prospective, randomized trial evaluating the prophylactic use of balloon pumping in high risk myocardial infarction patients: PAMI-2. *J Am Coll Cardiol*. 1995;25:86A [715-2]. Abstract.
  297. Goldberg RJ, Seeley D, Becker RC, et al. Impact of atrial fibrillation on the in-hospital and long-term survival of patients with acute myocardial infarction: a community-wide perspective. *Am Heart J*. 1990;119:996-1001.
  298. Behar S, Zahavi Z, Goldbourt U, Reicher-Reiss H. Long-term prognosis of patients with paroxysmal atrial fibrillation complicating acute myocardial infarction: SPRINT Study Group. *Eur Heart J*. 1992;13:45-50.
  299. Nielsen FE, Andersen HH, Gram-Hansen P, Sorensen HT, Klausen TC. The relationship between ECG signs of atrial infarction and the development of supraventricular arrhythmias in patients with acute myocardial infarction. *Am Heart J*. 1992;123:69-72.
  300. Kyriakis M, Barbetseas J, Antonopoulos A, Skouros C, Tentolouris C, Toutouzas P. Early atrial arrhythmias in acute myocardial infarction: role of the sinus node artery. *Chest*. 1992;101:944-947.
  301. Hildebrandt P, Jensen G, Kober L. Myocardial infarction 1979-1988 in Denmark: secular trends in age-related incidence, in-hospital mortality and complications. *Eur Heart J*. 1994;15:877-881.
  302. Waldo AL. An approach to therapy of supraventricular tachyarrhythmias: an algorithm versus individualized therapy. *Clin Cardiol*. 1994;17:II-21-II-26.
  303. Gardin JM, Singer DH. Atrial infarction: importance, diagnosis, and localization. *Arch Intern Med*. 1981;141:1345-1348.
  304. Liberthson RR, Salisbury KW, Hutter AM, Desancis RW. Atrial tachyarrhythmias in acute myocardial infarction. *Am J Med*. 1976;60:956-960.
  305. Kobayashi Y, Katoh T, Takano T, Hayakawa H. Paroxysmal atrial fibrillation and flutter associated with acute myocardial infarction: hemodynamic evaluation in relation to the development of arrhythmias and prognosis. *Jpn Circ J*. 1992;56:1-11.
  306. Nielsen FE, Sorensen HT, Christensen JH, Ravn L, Rasmussen SE. Reduced occurrence of atrial fibrillation in acute myocardial infarction treated with streptokinase. *Eur Heart J*. 1991;12:1081-1083.
  307. Hod H, Lew AS, Heltai M, et al. Early atrial fibrillation during evolving myocardial infarction: a consequence of impaired left atrial perfusion. *Circulation*. 1987;75:146-150.
  308. Rechavia E, Strasberg B, Mager A, et al. The incidence of atrial arrhythmias during inferior wall myocardial infarction with and without right ventricular involvement. *Am Heart J*. 1992;124:387-391.
  309. Behar S, Tanne D, Zion M, et al. Incidence and prognostic significance of chronic atrial fibrillation among 5839 consecutive patients with acute myocardial infarction: the SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial. *Am J Cardiol*. 1992;70:816-818.
  310. James TN. Myocardial infarction and atrial arrhythmias. *Circulation*. 1961;24:761-776.
  311. Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and myocardial infarction: a hypothesis formulated but not yet tested. *JAMA*. 1995;274:654-655.
  312. Kadish A, Morady F. The use of intravenous amiodarone in the acute therapy of life-threatening tachyarrhythmias. *Prog Cardiovasc Dis*. 1989;31:281-294.
  313. Campbell RWF. Arrhythmias. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction*. London, England: WB Saunders Co Ltd; 1994:223-240.
  314. Nordrehaug JE, von der Lippe G. Hypokalaemia and ventricular fibrillation in acute myocardial infarction. *Br Heart J*. 1983;50:525-529.
  315. Higham PD, Adams PC, Murray A, Campbell RW. Plasma potassium, serum magnesium and ventricular fibrillation: a prospective study. *Q J Med*. 1993;86:609-617.
  316. Volpi A, Cavalli A, Santoro E, Tognoni G. Incidence and prognosis of

- secondary ventricular fibrillation in acute myocardial infarction: evidence for a protective effect of thrombolytic therapy. GISSI Investigators. *Circulation*. 1990;82:1279-1288.
317. Campbell RW, Murray A, Julian DG. Ventricular arrhythmias in first 12 hours of acute myocardial infarction: natural history study. *Br Heart J*. 1981;46:351-357.
318. Antman EM, Berlin JA. Declining incidence of ventricular fibrillation in myocardial infarction: implications for the prophylactic use of lidocaine. *Circulation*. 1992;86:764-773.
319. Bechar S, Goldbourt U, Reicher-Reiss H, Kaplinsky E. Prognosis of acute myocardial infarction complicated by primary ventricular fibrillation: principal investigators of the SPRINT Study. *Am J Cardiol*. 1990;66:1208-1211.
320. Lown B, Fakhro AM, Hood WB Jr, Thorn GW. The coronary care unit: new perspectives and directions. *JAMA*. 1967;199:188-198.
321. Dharandhar RW, MacMillan RL, Brown KW. Primary ventricular fibrillation complicating acute myocardial infarction. *Am J Cardiol*. 1971;27:347-351.
322. El-Sherif N, Myerburg RJ, Scherlag BJ, et al. Electrocardiographic antecedents of primary ventricular fibrillation: value of the R-on-T phenomenon in myocardial infarction. *Br Heart J*. 1976;38:415-422.
323. Lie KI, Wellens HJ, Durrer D. Characteristics and predictability of primary ventricular fibrillation. *Eur J Cardiol*. 1974;1:379-384.
324. Solomon SD, Ridker PM, Antman EM. Ventricular arrhythmias in trials of thrombolytic therapy for acute myocardial infarction: a meta-analysis. *Circulation*. 1993;88:2575-2581.
325. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA*. 1988;260:1910-1916.
326. Emergency Cardiac Care Committee and Subcommittee, American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care, part III: adult advanced cardiac life support. *JAMA*. 1992;268:2199-2241.
327. Grande P. The Danish multicenter randomized study of invasive versus conservative treatment in patients with recurrent ischemia following thrombolysis in acute myocardial infarction: the Danish Acute Myocardial Infarction Trial (DANAMI). *Lancet*. In press.
328. Elder M, Sievner Z, Goldbourt U, et al. Primary ventricular tachycardia in acute myocardial infarction: clinical characteristics and mortality. The SPRINT Study Group. *Ann Intern Med*. 1992;117:31-36.
329. Wolfe CL, Nibley C, Bhandari A. Polymorphic ventricular tachycardia associated with acute myocardial infarction. *Circulation*. 1991;84:1543-1551.
330. Berger PB, Ruocco NA, Ryan TJ, Frederick MM, Podrid PJ. Incidence and significance of ventricular tachycardia and fibrillation in the absence of hypotension or heart failure in acute myocardial infarction treated with recombinant tissue-type plasminogen activator: results from the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. *J Am Coll Cardiol*. 1993;22:1773-1779.
331. Nademanee K, Taylor RD, Bailey WM. Management and long-term outcome of patients with electrical storm. *J Am Coll Cardiol*. 1995;25:187A. Abstract.
332. Scheinman MM, Levine JH, Cannon DS, et al. for the Intravenous Amiodarone Multicenter Investigators Group. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tacharyrhythmias. *Circulation*. 1995;92:3264-3272.
333. Berger PB, Ruocco NA Jr, Ryan TJ, Frederick MM, Jacobs AK, Faxon DP. Incidence and prognostic implications of heart block complicating inferior myocardial infarction treated with thrombolytic therapy: results from TIMI-II. *J Am Coll Cardiol*. 1992;20:533-540.
334. Nicod P, Gilpin E, Dittrich H, Polikar R, Henning H, Ross JJ. Long-term outcome in patients with inferior myocardial infarction and complete atrioventricular block. *J Am Coll Cardiol*. 1988;12:589-594.
335. McDonald K, O'Sullivan JJ, Conroy M, Robinson K, Mulcahy R. Heart block as predictor of in-hospital death in both acute inferior and acute anterior myocardial infarction. *Am J Med*. 1990;74:277-282.
336. Pasternak RC, Braunwald E, Sobel BE. Acute myocardial infarction. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, Pa: WB Saunders Co Ltd; 1992:1240-1249.
337. Fisch GR, Zipes DP, Fisch C. Bundle branch block in sudden death. *Prog Cardiovasc Dis*. 1980;23:187-224.
338. Hindman MC, Wagner GS, JaRo M, Atkins JM, Scheinman MM, DeSantis RW, Hutter AH Jr, Yeatman L, Rubenfire M, Pujura C, Rubin M, Morris JJ. The clinical significance of bundle branch block complicating acute myocardial infarction, I: clinical characteristics, hospital mortality, and one-year follow-up. *Circulation*. 1978;58:679-688.
339. DeGuzman M, Cavanish DT, Rahimtoola SH. AV node-His-Purkinje system disease: AV block (acute). In: Bogen E, Wilcock K, eds. *Clinical Cardiac Pacing*. Philadelphia, Pa: WB Saunders Co Ltd; 1995:321-332.
340. Varriale P, Inguaggiato A, David W. Bradyarrhythmias incident to thrombolysis for acute inferior wall infarction: a caveat. *Chest*. 1992;101:732-735.
341. Kent KM, Smith ER, Redwood DR, Epstein SE. Electrical stability of acutely ischemic myocardium: influences of heart rate and vagal stimulation. *Circulation*. 1973;47:291-298.
342. Antman EM. General hospital management. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction*. London, England: WB Saunders Co Ltd; 1994:57-59.
343. Zoll PM, Zoll RH, Falk RH, Clinton JE, Eitel DR, Antman EM. External noninvasive temporary cardiac pacing: clinical trials. *Circulation*. 1985;71:937-944.
344. Harthorne JW, Barold SS. Atherosclerosis, the conduction system, and cardiac pacing. In: Fuster V, Ross R, Topol EJ, eds. *Atherosclerosis and Coronary Artery Disease*. Philadelphia, Pa: Lippincott-Raven Publishers; 1996.
345. Wood MA. Temporary transvenous pacing. In: Ellenbogen KA, Kay GN, Wilkoff BL, eds. *Clinical Cardiac Pacing*. Philadelphia, Pa: WB Saunders Co Ltd; 1995:687-700.
346. Topol EJ, Goldsler N, Ports TA, et al. Hemodynamic benefit of atrial pacing in right ventricular myocardial infarction. *Ann Intern Med*. 1982;96:594-597.
347. Maveric Z, Zaputovic L, Matana A, et al. Prognostic significance of complete atrioventricular block in patients with acute inferior myocardial infarction with and without right ventricular involvement. *Am Heart J*. 1990;119:823-828.
348. Hynes JK, Holmes DR, Harrison CE. Five-year experience with temporary pacemaker therapy in the coronary care unit. *Mayo Clin Proc*. 1983;58:122-126.
349. Dreifus LS, Fisch C, Griffin JC, Gillette PC, Mason JW, Parsonnet V. Guidelines for implantation of cardiac pacemakers and antiarrhythmic devices: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Pacemaker Implantation). *J Am Coll Cardiol*. 1991;18:1-13.
350. Craver JM, Weintraub WS, Jones EL, Guyton RA, Hatcher CR Jr. Emergency coronary artery bypass surgery for failed percutaneous coronary angioplasty: a 10-year experience. *Ann Surg*. 1992;215:425-434.
351. Borkon AM, Failing TL, Piehler JM, Killen DA, Hoskins ML, Reed WA. Risk analysis of operative intervention for failed coronary angioplasty. *Ann Thorac Surg*. 1992;54:884-890.
352. Gersh BJ, Chesebro JH, Braunwald E, et al. Coronary artery bypass graft surgery after thrombolytic therapy in the Thrombolysis in the Myocardial Infarction Trial, Phase II (TIMI II). *J Am Coll Cardiol*. 1995;25:395-402.
353. Holmes DR, Calif RM, Topol EJ. Lessons we have learned from the GUSTO trial: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries. *J Am Coll Cardiol*. 1995;25(suppl 7):10S-17S.
354. Kereiakes DJ, Topol EJ, George BS, et al. Favorable early and long-term prognosis following coronary bypass surgery therapy for myocardial infarction: results of a multicenter trial. TAMI Study Group. *Am Heart J*. 1989;118:199-207.
355. Skinner JR, Phillips SJ, Zeff RH, Kongthaworn C. Immediate coronary bypass following failed streptokinase infusion in evolving myocardial infarction. *J Thorac Cardiovasc Surg*. 1984;87:567-570.
356. Barner HB, Lea JW IV, Naunheim KS, Stoney WS Jr. Emergency coronary bypass not associated with preoperative cardiogenic shock in failed angioplasty, after thrombolysis, and for acute myocardial infarction. *Circulation*. 1989;79(suppl 1):I-152-I-159.
357. Efstratiadis T, Munsch C, Crossman D, Taylor K. Aprotinin used in emergency coronary operation after streptokinase treatment. *Ann Thorac Surg*. 1991;52:1320-1321.
358. Breyer RH, Engelman RM, Rousou JA, Lemeshow S. Postinfarction angina: an expanding subset of patients undergoing coronary artery bypass. *J Thorac Cardiovasc Surg*. 1985;90:532-540.
359. Hochberg MS, Parsonnet V, Gielchinsky I, Hussain SM, Fisch DA, Norman JC. Timing of coronary revascularization after acute myocardial infarction:

- early and late results in patients revascularized within seven weeks. *J Thorac Cardiovasc Surg.* 1984;88:914-921.
360. Fremes SE, Goldman BS, Weisel RD, et al. Recent preoperative myocardial infarction increases the risk of surgery for unstable angina. *J Card Surg.* 1991;6:2-12.
  361. Kennedy JW, Ivey TD, Misbach G, et al. Coronary artery bypass graft surgery early after acute myocardial infarction. *Circulation.* 1989;79(suppl I):I-73-I-78.
  362. Floten HS, Ahmad A, Swanson JS, et al. Long-term survival after postinfarction bypass operation: early versus late operation. *Ann Thorac Surg.* 1989;48:757-762.
  363. Sintek CF, Pfeffer TA, Khonsari S. Surgical revascularization after acute myocardial infarction: does timing make a difference? *J Thorac Cardiovasc Surg.* 1994;107:1317-1321.
  364. Creswell LL, Moulton MJ, Cox JL, Rosenbloom M. Revascularization after acute myocardial infarction. *Ann Thorac Surg.* 1995;60:19-26.
  365. Kaul TK, Fields BL, Riggins SL, Dacumos GC, Wyatt DA, Jones CR. Coronary artery bypass grafting within 30 days of an acute myocardial infarction. *Ann Thorac Surg.* 1995;59:1169-1176.
  366. Gunnar RM, Loeb HS, Scanlon PJ, Moran JF, Johnson SA, Pifarre R. Management of acute myocardial infarction and accelerating angina. *Prog Cardiovasc Dis.* 1979;22:1-30.
  367. Loop FD, Lytle BW, Cosgrove DM, et al. Reoperation for coronary atherosclerosis: changing practice in 2509 consecutive patients. *Ann Surg.* 1990;212:378-385.
  368. Dittrich HC, Gilpin E, Nicod P, et al. Outcome after acute myocardial infarction in patients with prior coronary artery bypass surgery. *Am J Cardiol.* 1993;72:507-513.
  369. Reul GJ, Cooley DA, Hallman GL, et al. Coronary artery bypass for unsuccessful percutaneous transluminal coronary angioplasty. *J Thorac Cardiovasc Surg.* 1984;88:685-694.
  370. Golding LA, Loop FD, Hollman JL, et al. Early results of emergency surgery after coronary angioplasty. *Circulation.* 1986;74(suppl III):III-26-III-29.
  371. Mooney MR, Arom KV, Joyce LD, et al. Emergency cardiopulmonary bypass support in patients with cardiac arrest. *J Thorac Cardiovasc Surg.* 1991;101:450-454.
  372. Beyersdorf F, Buckberg GD. Myocardial protection in patients with acute myocardial infarction and cardiogenic shock. *Semin Thorac Cardiovasc Surg.* 1993;5:151-161.
  373. Bottner RK, Wallace RB, Visner MS, et al. Reduction of myocardial infarction after emergency coronary artery bypass grafting for failed coronary angioplasty with use of a normothermic reperfusion cardioplegia protocol. *J Thorac Cardiovasc Surg.* 1991;101:1069-1075.
  374. Lichtenstein SV, Abel JG, Salerno TA. Warm heart surgery and results of operation for recent myocardial infarction. *Ann Thorac Surg.* 1991;52:455-458.
  375. Akins CW. Early and late results following emergency isolated myocardial revascularization during hypothermic fibrillatory arrest. *Ann Thorac Surg.* 1987;43:131-137.
  376. Akins CW. 1987: early and late results following emergency isolated myocardial revascularization during hypothermic fibrillatory arrest. Updated in 1994 by Cary W. Akins, MD. *Ann Thorac Surg.* 1994;58:1205-1206.
  377. Guyton RA, Arcidi JM Jr, Langford DA, Morris DC, Liberman HA, Hatcher CR Jr. Emergency coronary bypass for cardiogenic shock. *Circulation.* 1987;76(suppl V):V-22-V-27.
  378. Zapolanski A, Pliam MB, Bronstein MH, et al. Arterial conduits in emergency coronary artery surgery. *J Card Surg.* 1995;10:32-39.
  379. Clements SD Jr, Story WE, Hurst JW, Craver JM, Jones EL. Ruptured papillary muscle, a complication of myocardial infarction: clinical presentation, diagnosis, and treatment. *Clin Cardiol.* 1985;8:93-103.
  380. Tepe NA, Edmunds LH Jr. Operation for acute postinfarction mitral insufficiency and cardiogenic shock. *J Thorac Cardiovasc Surg.* 1985;89:525-530.
  381. Kishon Y, Oh JK, Schaff HV, Mullany CJ, Tajik AJ, Gersh BJ. Mitral valve operation in post-infarction rupture of a papillary muscle: immediate results and long-term follow-up of 22 patients. *Mayo Clin Proc.* 1992;67:1023-1030.
  382. Hendren WG, Nemec JJ, Lytle BW, et al. Mitral valve repair for ischemic mitral insufficiency. *Ann Thorac Surg.* 1991;52:1246-1251.
  383. Westaby S, Parry A, Ormerod O, Gooneratne P, Pillai R. Thrombolysis and postinfarction ventricular septal rupture. *J Thorac Cardiovasc Surg.* 1992;104:1506-1509.
  384. Lemery R, Smith HC, Giuliani ER, Gersh BJ. Prognosis in rupture of the ventricular septum after acute myocardial infarction and role of early surgical intervention. *Am J Cardiol.* 1992;70:147-151.
  385. Skillington PD, Davies RH, Luff AJ, et al. Surgical treatment for infarct-related ventricular septal defects: improved early results combined with analysis of late functional status. *J Thorac Cardiovasc Surg.* 1990;99:798-808.
  386. Muehrcke DD, Daggett WM Jr, Buckley MJ, Akins CW, Hilgenberg AD, Austen WG. Postinfarct ventricular septal defect repair: effect of coronary artery bypass grafting. *Ann Thorac Surg.* 1992;54:876-882.
  387. Padro JM, Mesa JM, Silvestre J, et al. Subacute cardiac rupture: repair with a sutureless technique. *Ann Thorac Surg.* 1993;55:20-23.
  388. Mills NL, Everson CT, Hockmuth DR. Technical advances in the treatment of left ventricular aneurysm. *Ann Thorac Surg.* 1993;55:792-800.
  389. Komeda M, David TE, Malik A, Ivanov J, Sun Z. Operative risks and long-term results of operation for left ventricular aneurysm. *Ann Thorac Surg.* 1992;53:22-28.
  390. Farrar DJ, Hill JD. Univentricular and biventricular Thoratec VAD support as a bridge to transplantation. *Ann Thorac Surg.* 1993;55:276-282.
  391. Moritz A, Wolner E. Circulatory support with shock due to acute myocardial infarction. *Ann Thorac Surg.* 1993;55:238-244.
  392. Lick S, Copeland JG III, Smith RG, et al. Use of the Symbion biventricular assist device in bridging to transplantation. *Ann Thorac Surg.* 1993;55:283-287.
  393. Lincoff AM, Popma JJ, Bates ER, et al. Successful coronary angioplasty in two patients with cardiogenic shock using the Nimbus Hemopump support device. *Am Heart J.* 1990;120:970-972.
  394. Gacioch GM, Ellis SG, Lee L, et al. Cardiogenic shock complicating acute myocardial infarction: the use of coronary angioplasty and the integration of the new support devices into patient management. *J Am Coll Cardiol.* 1992;19:647-653.
  395. Smalling RW, Sweeney M, Lachterman B, et al. Transvalvular left ventricular assistance in cardiogenic shock secondary to acute myocardial infarction: evidence for recovery from near fatal myocardial stunning. *J Am Coll Cardiol.* 1994;23:637-644.
  396. Shawl FA, Domanski MJ, Hernandez TJ, Punja S. Emergency percutaneous cardiopulmonary bypass support in cardiogenic shock from acute myocardial infarction. *Am J Cardiol.* 1989;64:967-970.
  397. Joyce LD, Johnson KE, Toninato CJ, et al. Results of the first 100 patients who received Symbion total artificial hearts as a bridge to cardiac transplantation. *Circulation.* 1989;80(suppl III):III-192-III-201.
  398. Champagnac D, Claudel JP, Chevalier P, et al. Primary cardiogenic shock during acute myocardial infarction: results of emergency cardiac transplantation. *Eur Heart J.* 1993;14:925-929.
  399. Hannan EL, O'Donnell JF, Kilburn H Jr, Bernard HR, Yazici A. Investigation of the relationship between volume and mortality for surgical procedures performed in New York State hospitals. *JAMA.* 1989;262:503-510.
  400. Hannan EL, Siu AL, Kumar D, Kilburn H Jr, Chassin MR. The decline in coronary artery bypass graft surgery mortality in New York State: the role of surgeon volume. *JAMA.* 1995;273:209-213.
  401. Showstack JA, Rosenfeld KE, Garnick DW, Luft HS, Schaffarzick RW, Fowles J. Association of volume with outcome of coronary artery bypass graft surgery: scheduled vs nonscheduled operations. *JAMA.* 1987;257:785-789.
  402. Fung HL, Chung SJ, Bauer JA, Chong S, Kowaluk EA. Biochemical mechanism of organic nitrate action. *Am J Cardiol.* 1992;70(suppl 5):4B-10B.
  403. Luscher TF. Endothelium-derived nitric oxide: the endogenous nitrovasodilator in the human cardiovascular system. *Eur Heart J.* 1991;12(suppl E):2-11.
  404. Abrams J. Hemodynamic effects of nitroglycerin and long-acting nitrates. *Am Heart J.* 1985;110:216-224.
  405. Winbury MM. Redistribution of left ventricular blood flow produced by nitroglycerin: an example of integration of the macro- and microcirculation. *Circ Res.* 1971;28(suppl I):140-147.
  406. Gorman MW, Sparks HV Jr. Nitroglycerin causes vasodilatation within ischaemic myocardium. *Cardiovasc Res.* 1980;14:515-521.

407. Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT. The mechanisms of nitroglycerin action: stenosis vasodilatation as a major component of the drug response. *Circulation*. 1981;64:1089-1097.
408. Needleman P, Jakschik B, Johnson EM Jr. Sulphydryl requirement for relaxation of vascular smooth muscle. *J Pharmacol Exp Ther*. 1973;187:324-331.
409. Abrams J. The role of nitrates in coronary heart disease. *Arch Intern Med*. 1995;155:357-364.
410. Gunnar RM, Lambrew CT, Abrams W, et al. Task force IV: pharmacologic interventions. Emergency cardiac care. *Am J Cardiol*. 1982;50:393-408.
411. Needleman P, Johnson EM Jr. Mechanism of tolerance development to organic nitrates. *J Pharmacol Exp Ther*. 1973;184:709-715.
412. Munzel T, Sayegh H, Freeman BA, Tarpey MM, Harrison DG. Evidence for enhanced vascular superoxide anion production in nitrate tolerance: a novel mechanism underlying tolerance and cross-tolerance. *J Clin Invest*. 1995;95:187-194.
413. Thadani U, Maranda CR, Amsterdam E, et al. Lack of pharmacologic tolerance and rebound angina pectoris during twice-daily therapy with isosorbide-5-mononitrate. *Ann Intern Med*. 1994;120:353-359.
414. Becker RC, Corrao JM, Bovill EG, et al. Intravenous nitroglycerin-induced heparin resistance: a qualitative antithrombin III abnormality. *Am Heart J*. 1990;119:1254-1261.
415. Bode V, Welzel D, Franz G, Polensky U. Absence of drug interaction between heparin and nitroglycerin: randomized placebo-controlled crossover study. *Arch Intern Med*. 1990;150:2117-2119.
- 415a. Gonzalez ER, Jones HD, Graham S, Elswick RK. Assessment of the drug interaction between intravenous nitroglycerin and heparin. *Ann Pharmacother*. 1992;26:1512-1514.
416. Bussmann WD, Passek D, Seidel W, Kaltenbach M. Reduction of CK and CK-MB indexes of infarct size by intravenous nitroglycerin. *Circulation*. 1981;63:615-622.
417. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications: effect of timing, dosage, and infarct location. *Circulation*. 1988;78:906-919.
418. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. *Lancet*. 1988;1:1088-1092.
419. Fitzgerald LG, Bennett ED. The effects of oral isosorbide mononitrate on mortality following acute myocardial infarction: a multicenter study. *Eur Heart J*. 1990;11:120-126.
420. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction: Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet*. 1994;343:1115-1122.
421. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet*. 1995;345:669-685.
422. Fuster V, Dyken ML, Vokonas PS, Hennekens C. Aspirin as a therapeutic agent in cardiovascular disease. *Circulation*. 1993;87:659-675.
423. Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy. *Chest*. 1995;108(suppl):225S-522S.
424. Burch JW, Stanford N, Majerus PW. Inhibition of platelet prostaglandin synthetase by oral aspirin. *J Clin Invest*. 1978;61:314-319.
425. Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets, I: acetylation of a particulate fraction protein. *J Clin Invest*. 1975;56:624-632.
426. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol*. 1971;231:232-235.
427. Moncada S, Vane JR. The role of prostacyclin in vascular tissue. *Fed Proc*. 1979;38:66-71.
428. Buchanan MR, Dejana E, Cazenave JP, Richardson M, Mustard JF, Hirsh J. Differences in inhibition of PG12 production by aspirin in rabbit artery and vein segments. *Thromb Res*. 1980;20:447-460.
429. Jaffe EA, Weksler BB. Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin. *J Clin Invest*. 1979;63:532-535.
430. Hennekens CH, Peto R, Hutchison GB, Doll R. An overview of the British and American aspirin studies. *N Engl J Med*. 1988;318:923-924.
431. Hirsh J, Dalen JE, Fuster V, Harker LB, Salzman EW. Aspirin and other platelet-active drugs: the relationship between dose, effectiveness, and side effects. *Chest*. 1992;102(suppl 4):327S-336S.
432. Leonards JR, Levy G. Effect of pharmaceutical formulation on gastrointestinal bleeding from aspirin tablets. *Arch Intern Med*. 1972;129:457-460.
433. MacKercher PA, Ivey KJ, Baskin WN, Krause WJ. Protective effect of cimetidine on aspirin-induced gastric mucosal damage. *Ann Intern Med*. 1977;87:676-679.
434. Bowen BK, Krause WJ, Ivey KJ. Effect of sodium bicarbonate on aspirin-induced damage and potential difference changes in human gastric mucosa. *Br Med J*. 1977;2:1052-1055.
435. Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med*. 1986;104:390-398.
436. Mielants H, Verbruggen G, Schelstraete K, Veys EM. Salicylate-induced gastrointestinal bleeding: comparison between soluble buffered, enteric-coated, and intravenous administration. *J Rheumatol*. 1979;6:210-218.
437. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation*. 1988;77:1324-1332.
438. Chesebro JH, Clements IP, Fuster V, et al. A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. *N Engl J Med*. 1982;307:73-78.
439. Sanz G, Pajaron A, Alegria E, et al. Prevention of early aortocoronary bypass occlusion by low-dose aspirin and dipyridamole: Grupo Espanol para el Seguimiento del Injerto Coronario (GESIC). *Circulation*. 1990;82:765-773.
440. Goldman S, Copeland J, Moritz T, et al. Starting aspirin therapy after operation: effects on early graft patency: Department of Veterans Affairs Cooperative Study Group. *Circulation*. 1991;84:520-526.
441. Balsano F, Rizzon P, Violi F, et al. Antiplatelet treatment with ticlopidine in unstable angina: a controlled multicenter clinical trial: the Studio della Ticlopidina nell'Angina Instabile Group. *Circulation*. 1990;82:17-26.
442. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *JAMA*. 1912;59:2015.
443. Chazov EI, Matveeva LS, Mazaev AV, Sargin KE, Sadovskia GV, Ruda MI. Intracoronary administration of fibrinolysis in acute myocardial infarct. *Ter Arkh*. 1976;48:8-19.
444. Rentrop KP, Blanke H, Karsch KR, et al. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. *Clin Cardiol*. 1979;2:354-363.
445. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation*. 1981;63:307-317.
446. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis: characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J*. 1983;50:127-134.
447. Davies MJ, Thomas AC. Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J*. 1985;53:363-373.
448. Mizuno K, Satomura K, Miyamoto A, et al. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med*. 1992;326:287-291.
449. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The waveform phenomenon of ischemic cell death. I: myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation*. 1977;56:786-794.
450. Anderson JL, Marshall HW, Bray BE, et al. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med*. 1983;308:1312-1318.
451. Khaja F, Walton JA Jr, Brymer JF, et al. Intracoronary fibrinolytic therapy in acute myocardial infarction: report of a prospective randomized trial. *N Engl J Med*. 1983;308:1305-1311.
452. Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz JK. The western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12-month follow-up report. *N Engl J Med*. 1985;312:1073-1078.
453. Sheehan FH, Mathey DG, Schofer J, Dodge HT, Bolson EL. Factors that determine recovery of left ventricular function after thrombolysis in patients with acute myocardial infarction. *Circulation*. 1985;71:1121-1128.
454. Sherry S. Personal reflections on the development of thrombolytic therapy and its application to acute coronary thrombosis. *Am Heart J*. 1981;102:1134-1138.
455. Fletcher AP, Alkjaersig N, Smyrniotis FE, Sherry S. The treatment of

- patients suffering from early myocardial infarction with massive and prolonged streptokinase therapy. *Trans Assoc Am Physicians*. 1958;71:287.
456. Schroder R, Biamino G, von Leitner ER, et al. Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation*. 1983;67:536-548.
  457. Rogers WJ, Mantle JA, Hood WP Jr, et al. Prospective randomized trial of intravenous and intracoronary streptokinase in acute myocardial infarction. *Circulation*. 1983;68:1051-1061.
  458. Anderson JL, Marshall HW, Askins JC, et al. A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. *Circulation*. 1984;70:606-618.
  459. Sherry S. *Fibrinolysis, Thrombosis, and Hemostasis: Concepts, Perspectives, and Clinical Applications*. Philadelphia, Pa: Lea & Febiger; 1992:119-160.
  460. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet*. 1988;2:525-530.
  461. AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. *Lancet*. 1990;335:427-431.
  462. The International Study Group. In-hospital mortality and clinical course of 20 891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet*. 1990;336:71-75.
  463. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction: ISIS-3. *Lancet*. 1992;339:753-770.
  464. Anderson JL, Karagounis LA. Does intravenous heparin or time-to-treatment/reperfusion explain differences between GUSTO and ISIS-3 results? *Am J Cardiol*. 1994;74:1057-1060.
  465. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med*. 1993;329:1615-1622.
  466. Simes RJ, Topol EJ, Holmes DR, et al. for the GUSTO-I Investigators. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. *Circulation*. 1995;91:1923-1928.
  467. Neuhaus KL, Feuerer W, Jeep-Tebbe S, Niederer W, Vogt A, Tebbe U. Improved thrombolysis with a modified dose regimen of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol*. 1989;14:1566-1569.
  468. Cannon CP, McCabe CH, Diver DJ, et al. Comparison of front-loaded recombinant tissue-type plasminogen activator, anistreplase and combination thrombolytic therapy for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. *J Am Coll Cardiol*. 1994;24:1602-1610.
  469. Fuster V. Coronary thrombolysis: a perspective for the practicing physician. *N Engl J Med*. 1993;329:723-725.
  470. Simoons ML, Arnold AE. Tailored thrombolytic therapy: a perspective. *Circulation*. 1993;88:2556-2564.
  471. White HD. Selecting a thrombolytic agent. *Cardiol Clin*. 1995;13:347-354.
  472. Rogers WJ, Chandra NC, French WJ, Gore JM, Lambrew CT, Tiefenbrunn AJ. Trends in the use of reperfusion therapy: experience from the Second National Registry of Myocardial Infarction (NRMI 2). *Circulation*. In press.
  - 472a. French JK, Williams BF, Hart HH, et al. Prospective evaluation of eligibility for thrombolytic therapy in acute myocardial infarction. *BMJ* 1996;312:1637-1641.
  473. Hirsh J. Heparin. *N Engl J Med*. 1991;324:1565-1574.
  474. MacMahon S, Collins R, Knight C, Yusuf S, Peto R. Reduction in major morbidity and mortality by heparin in acute myocardial infarction. *Circulation*. 1988;78(suppl II)-98. Abstract.
  475. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 1988;11:1-11.
  476. Popma JJ, Calif RM, Ellis SG, George BS, et al. Mechanism of benefit of combination thrombolytic therapy for acute myocardial infarction: a quantitative angiographic and hematologic study. *J Am Coll Cardiol*. 1992;20:1305-1312.
  477. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. *Lancet*. 1990;336:65-71.
  478. Col J, Decoster O, Hanique G, et al. Infusion of heparin conjunct to streptokinase accelerates reperfusion of acute myocardial infarction: results of a double blind randomized study (OSIRIS). *Circulation*. 1992;86(suppl I):I-259. Abstract.
  479. Melandri G, Branzi A, Semprini F, Cervi V, Galie N, Magnani B. Enhanced thrombolytic efficacy and reduction of infarct size by simultaneous infusion of streptokinase and heparin. *Br Heart J*. 1990;64:118-120.
  480. O'Connor CM, Meese R, Carney R, et al. A randomized trial of intravenous heparin in conjunction with anistreplase (anisoylated plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University Clinical Cardiology Study (DUCCS) 1. *J Am Coll Cardiol*. 1994;23:11-18.
  481. White HD, Yusuf S. Issues regarding the use of heparin following streptokinase therapy. *J Thrombosis Thrombolysis*. 1995;2:5-10.
  482. The SCATI Group. Randomised controlled trial of subcutaneous calcium-heparin in acute myocardial infarction: the SCATI (Studio sulla Calciparina nell'Angina e nella Thrombosi ventricolare nell'Infarto) group. *Lancet*. 1989;2:182-186.
  483. Bleich SD, Nichols TC, Schumacher RR, Cooke DH, Tate DA, Teichman SL. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. *Am J Cardiol*. 1990;66:1412-1417.
  484. de Bono DP, Simoons ML, Tijssen J, et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J*. 1992;67:122-128.
  485. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction: Heparin-Aspirin Reperfusion Trial (HART) Investigators. *N Engl J Med*. 1990;323:1433-1437.
  486. Mahaffey KW, Granger CB, Collins R, et al. Overview of randomized trials of intravenous heparin in patients with acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol*. 1996;77:551-556.
  487. Ogilby JD, Kopelman HA, Klein LW, Agarwal JB. Adequate heparinization during PTCA: assessment using activated clotting times. *Cathet Cardiovasc Diagn*. 1989;18:206-209.
  488. Narins CR, Hillegass WB, Nelson CL, et al. Relation between activated clotting time during angioplasty and abrupt closure. *Circulation*. 1996;93:667-671.
  489. The Epic Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
  490. Topol EJ, Calif RM, Weissman HF. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet*. 1994;343:881-886.
  491. Moliterno DJ, Calif RM, Aguirre FV, et al. Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (the EPIC trial). *J Am Coll Cardiol*. 1995;75:559-562.
  492. Lincoff AM. Evaluation of PTCA to improve long-term outcomes by c7E3 glycoprotein IIb/IIIa receptor blockade (EPILOG). Presented at the American College of Cardiology Annual Scientific Session; March 1996; Orlando, Fla.
  493. Simoons ML. Refractory unstable angina: reduction of events by c7E3: the CAPTURE Study. Presented at the American College of Cardiology Annual Scientific Session; March 1996; Orlando, Fla.
  494. Granger CB, Hirsh J, Calif RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I Trial. *Circulation*. 1996;93:870-878.
  495. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. *Circulation*. 1994;90:1631-1637.
  496. Antman EM. Hirudin in acute myocardial infarction: safety report from the

- Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. *Circulation*. 1994;90:1624-1630.
497. Zabel KM, Granger CB, Becker RC, Woodlief LH, Chesebro JH, Calif RM. Bedside aPTT monitoring is associated with less bleeding among GUSTO patients receiving i.v. heparin following thrombolytic administration. *J Am Coll Cardiol*. In press.
498. Chesebro JH, Fuster V. Antithrombotic therapy for acute myocardial infarction: mechanisms and prevention of deep venous, left ventricular, and coronary artery thromboembolism. *Circulation*. 1986;74(suppl III):III-1-III-10.
499. Thompson PL, Aylward PE, Federman J, et al. A randomized comparison of intravenous heparin with oral aspirin and dipyridamole 24 hours after recombinant tissue-type plasminogen activator for acute myocardial infarction. *Circulation*. 1991;83:1534-1542.
500. Granger CB, Miller JM, Bovill EG, et al. Rebound increase in thrombin generation and activity after cessation of intravenous heparin in patients with acute coronary syndromes. *Circulation*. 1995;91:1929-1935.
501. Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med*. 1992;327:141-145.
502. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330-1335.
503. Harrington RA, Sane DC, Calif RM, et al. Clinical importance of thrombocytopenia occurring in the hospital phase after administration of thrombolytic therapy for acute myocardial infarction: the Thrombolysis and Angioplasty in Myocardial Infarction Study Group. *J Am Coll Cardiol*. 1994;23:891-898.
504. Hirsh J, Raschke R, Warkentin TE, Dalen JE, Deykin D, Poller L. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest*. 1995;108(suppl):258S-275S.
505. Hirsh J, Fuster V. Guide to anticoagulant therapy, part 1: heparin. *Circulation*. 1994;89:1449-1468. AHA medical/scientific statement.
506. FRISC Study Group. Low-molecular-weight heparin during instability in coronary artery disease: Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. *Lancet*. 1996;347:561-568.
507. Gurfinkel EP, Munos EJ, Mejail RI, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol*. 1995;26:313-318.
508. Turpie AG, Gent M, Cote R, et al. A low-molecular-weight heparinoid compared with unfractionated heparin in the prevention of deep vein thrombosis in patients with acute ischemic stroke: a randomized, double-blind study. *Ann Intern Med*. 1992;117:353-357.
509. Cannon CP, McCabe CH, Henry TD, et al. A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. *J Am Coll Cardiol*. 1994;23:993-1003.
510. Lee LV. Initial experience with hirudin and streptokinase in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 6 trial. *Am J Cardiol*. 1995;75:7-13.
511. Lefkovits J, Topol EJ. Direct thrombin inhibitors in cardiovascular medicine. *Circulation*. 1994;90:1522-1536.
512. Topol EJ. Global use of strategies to open coronary arteries (GUSTO II): hirudin vs heparin in acute coronary syndromes. Presented at the American College of Cardiology Annual Scientific Session; March 1996; Orlando, Fla.
- 512a. Antman EM, for the TIMI 9B Investigators. Hirudin in acute myocardial infarction: Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B Trial. *Circulation*. 1996;94:911-921.
513. Anderson JL. Antiarrhythmics. In: Williams RL, Brater DC, Mardent J, eds. *Rational Therapeutics: A Clinical Pharmacologic Guide for the Health Professional*. New York, NY: Marcel Dekker Inc; 1990:339-381.
514. Lie KI, Wellens HJ, van Capelle FJ, Durrer D. Lidocaine in the prevention of primary ventricular fibrillation: a double-blind, randomized study of 212 consecutive patients. *N Engl J Med*. 1974;291:1324-1326.
515. Valentine PA, Frew JL, Mashford ML, Sloman JG. Lidocaine in the prevention of sudden death in the pre-hospital phase of acute infarction: a double-blind study. *N Engl J Med*. 1974;291:1327-1331.
516. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA*. 1993;270:1589-1595.
517. Hazinski MF, Cummins RO, eds. *1996 Handbook of Emergency Cardiac Care for Healthcare Providers*. Dallas, Tex: American Heart Association; 1996.
518. Haynes RE, Chinn TL, Copass MK, Cobb LA. Comparison of bretylium tosylate and lidocaine in management of out-of-hospital ventricular fibrillation: a randomized clinical trial. *Am J Cardiol*. 1981;48:353-356.
519. Olson DW, Thompson BM, Darin JC, Milbrath MH. A randomized comparison study of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. *Ann Emerg Med*. 1984;13:807-810.
520. Anderson JL. Sotalol, bretylium, and other class III antiarrhythmic agents. In: Podrid PJ, Kowey PR, eds. *Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management*. Baltimore, Md: Williams & Wilkins; 1995:450-465.
521. Deedwania P. *Beta-Blockers and Cardiac Arrhythmias*. New York, NY: Marcel Dekker Inc; 1992.
522. Naccarelli GV, Dougherty AH. Amiodarone: a review of its pharmacologic antiarrhythmic and adverse effects. In: Podrid PJ, Kowey PR, eds. *Cardiac Arrhythmia: Mechanisms, Diagnosis, and Management*. Baltimore, Md: Williams & Wilkins; 1995:434-449.
523. Kowey PR, for the IV Amiodarone Investigators. A multicenter randomized double-blind comparison of intravenous bretylium with amiodarone in patients with frequent, malignant ventricular arrhythmia. *Circulation*. 1993;88(suppl I):I-396. Abstract.
524. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27:335-371.
525. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet*. 1986;2:57-66.
526. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction: patient population. *Am J Cardiol*. 1985;56:1G-57G.
527. Sigurdsson A, Swedberg K. Left ventricular remodelling, neurohormonal activation and early treatment with enalapril (CONSENSUS II) following myocardial infarction. *Eur Heart J*. 1994;15(suppl B):14-19.
528. Pfeffer MA, Hennekens CH. When a question has an answer: rationale for our early termination of the HEART Trial. *Am J Cardiol*. 1995;75:1173-1175.
529. Latini R, Maggioni AP, Flather M, Sleight P, Tognoni G. ACE-inhibitor use in patients with myocardial infarction: summary of evidence from clinical trials. *Circulation*. 1995;92:3132-3137.
530. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction: the Survival of Myocardial Infarction: Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med*. 1995;332:80-85.
531. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet*. 1995;345:686-687.
532. Furberg CD, Psaty BM, Mayer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation*. 1995;92:1326-1331.
533. Muller JE, Morrison J, Stone PH, et al. Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. *Circulation*. 1984;69:740-747.
534. Sirnes PA, Overskeid K, Pedersen TR, et al. Evolution of infarct size during the early use of nifedipine in patients with acute myocardial infarction: the Norwegian Nifedipine Multicenter Trial. *Circulation*. 1984;70:638-644.
535. Wilcox RG, Hampton JR, Banks DC, et al. Trial of early nifedipine in acute myocardial infarction: the TRENT study. *Br Med J (Clin Res)*. 1986;293:1204-1208.
536. The Israeli Sprint Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT): a randomized intervention trial of nifedipine in patients with acute myocardial infarction. *Eur Heart J*. 1988;9:354-364.
537. Goldbourt U, Behar S, Reicher-Reiss H, Zion M, Mandelzweig L, Kaplinsky E. Early administration of nifedipine in suspected acute myocardial infarction: the Secondary Prevention Reinfarction Israel Nifedipine Trial 2 Study. *Arch Intern Med*. 1993;153:345-353.
538. Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. *Circulation*. 1995;92:1068-1073.
539. Verapamil in acute myocardial infarction: the Danish Study Group on Verapamil in Myocardial Infarction. *Eur Heart J*. 1984;5:516-528.
540. Gheorghiade M. Calcium channel blockers in the management of myocardial infarction patients. *Henry Ford Hosp Med J*. 1991;39:210-216.

541. Held PH, Yusuf S. Effects of beta-blockers and calcium channel blockers in acute myocardial infarction. *Eur Heart J*. 1993;14(suppl F):18-25.
542. Hilton TC, Miller DD, Kern MJ. Rational therapy to reduce mortality and reinfarction following myocardial infarction. *Am Heart J*. 1991;122:1740-1750.
543. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II—DAVIT II). *Am J Cardiol*. 1990;66:779-785.
544. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med*. 1988;319:385-392.
545. Gibson RS, Boden WE, Theroux P, et al. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med*. 1986;315:423-429.
546. Boden WE. Non-Q-wave myocardial infarction: a prognostic paradox. *Hosp Pract (Office)*. 1992;27:79-92.
547. Boden WE, Scheldewaert R, Walters EG, et al. Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (diltiazem) (INTERCEPT) Research Group: design of a placebo-controlled clinical trial of long-acting diltiazem and aspirin versus aspirin alone in patients receiving thrombolysis with a first acute myocardial infarction. *Am J Cardiol*. 1995;75:112U-1123.
548. Arsenian MA. Magnesium and cardiovascular disease. *Prog Cardiovasc Dis*. 1993;35:271-310.
549. Woods KL. Possible pharmacological actions of magnesium in acute myocardial infarction. *Br J Clin Pharmacol*. 1991;32:3-10.
550. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. *Am Heart J*. 1984;108:188-193.
551. Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. Mg<sup>2+</sup>-Ca<sup>2+</sup> interaction in contractility of vascular smooth muscle: Mg<sup>2+</sup> versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Can J Physiol Pharmacol*. 1987;65:729-745.
552. du Toit EF, Opie LH. Modulation of severity of reperfusion stunning in the isolated rat heart by agents altering calcium flux at onset of reperfusion. *Circ Res*. 1992;70:960-967.
553. Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ*. 1991;303:1499-1503.
554. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction. *JAMA*. 1992;268:240-248.
555. Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet*. 1992;339:1553-1558.
556. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet*. 1994;343:816-819.
557. Antman EM. Magnesium in acute MI: timing is critical. *Circulation*. 1995;92:2367-2372.
558. Antman EM. Randomized trials of magnesium in acute myocardial infarction: big numbers do not tell the whole story. *Am J Cardiol*. 1995;75:391-393.
559. Shechter M, Hod H, Chouraqui P, Kaplinsky E, Rabinowitz B. Magnesium therapy in acute myocardial infarction when patients are not candidates for thrombolytic therapy. *Am J Cardiol*. 1995;75:321-323.
560. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure: the PROMISE Study Research Group. *N Engl J Med*. 1991;325:1468-1475.
561. Gheorghiade M. A symposium: management of heart failure in the 1990s: a reassessment of the role of digoxin therapy. *Am J Cardiol*. June 4. 1992;69(18):1G-154G.
562. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors: RADIANCE study. *N Engl J Med*. 1993;329:1-7.
563. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial: PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22:955-962.
564. Gorlin R, Garg R. The effect of digitalis on morbidity and hospitalizations in patients with heart failure. Presented at the American College of Cardiology Annual Scientific Session; March 1996; Orlando, Fla.
565. DeBusk RF. Specialized testing after recent acute myocardial infarction. *Ann Intern Med*. 1989;110:470-481.
566. Schlant RC, Blomqvist CG, Brandenburg RO, et al. Guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Exercise Testing). *J Am Coll Cardiol*. 1986;8:725-738.
567. Ritchie JL, Bateman TM, Bonow RO, et al. ACC/AHA guidelines for clinical use of cardiac radionuclide imaging: report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. *J Am Coll Cardiol*. 1995;25:521-547.
568. Theroux P, Waters DD, Halphen C, Debaisieux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med*. 1979;301:341-345.
569. DeBusk RF, Kraemer HC, Nash E, Berger WE, Lew H. Stepwise risk stratification soon after acute myocardial infarction. *Am J Cardiol*. 1983;52:1161-1166.
570. Krone RJ, Gillespie JA, Weld FM, Miller JP, Moss AJ. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. *Circulation*. 1985;71:80-89.
571. Mark DB, Hlatky MA, Harrell FE, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med*. 1987;106:793-800.
572. Ross JJ, Gilpin EA, Madsen EB, et al. A decision scheme for coronary angiography after acute myocardial infarction. *Circulation*. 1989;79:292-303.
573. Rouleau JL, Talajic M, Sussex B, et al. Myocardial infarction patients in the 1990s—their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. *J Am Coll Cardiol*. 1996;27:1119-1127.
574. Rogers WJ, Babb JD, Baim DS, et al. Selective versus routine predischarge coronary arteriography after therapy with recombinant tissue-type plasminogen activator, heparin and aspirin for acute myocardial infarction: TIMI II Investigators. *J Am Coll Cardiol*. 1991;17:1007-1016.
575. Ritchie JL, Cerqueira M, Maynard C, Davis K, Kennedy JW. Ventricular function and infarct size: the Western Washington Intravenous Streptokinase in Myocardial Infarction Trial. *J Am Coll Cardiol*. 1988;11:689-697.
576. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. *N Engl J Med*. 1985;312:932-936.
577. Chaitman BR, McMahon RP, Terrin M, et al. Impact of treatment strategy on predischarge exercise test in the Thrombolysis in Myocardial Infarction (TIMI) II Trial. *Am J Cardiol*. 1993;71:131-138.
578. Villella A, Maggioni AP, Villella M, et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: the GISSI-2 data base. Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto. *Lancet*. 1995;346:523-529.
579. Mark DB, Shaw L, Harrell FE, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991;325:849-853.
580. Piccalo G, Pirelli S, Massa D, Cipriani M, Sarullo FM, De Vita C. Value of negative predischarge exercise testing in identifying patients at low risk after acute myocardial infarction treated by systemic thrombolysis. *Am J Cardiol*. 1992;70:31-33.
581. Hamm LF, Crow RS, Stull GA, Hannan P. Safety and characteristics of exercise testing early after acute myocardial infarction. *Am J Cardiol*. 1989;63:1193-1197.
582. Juneau M, Colles P, Theroux P, et al. Symptom-limited versus low level exercise testing before hospital discharge after myocardial infarction. *J Am Coll Cardiol*. 1992;20:927-933.
583. Jain A, Myers GH, Sapin PM, O'Rourke RA. Comparison of symptom-limited and low level exercise tolerance tests early after myocardial infarction. *J Am Coll Cardiol*. 1993;22:1816-1820.
584. Gibson RS, Watson DD, Craddock GB, et al. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. *Circulation*. 1983;68:321-336.

585. Hung J, Goris ML, Nash E, et al. Comparative value of maximal treadmill testing, exercise thallium myocardial perfusion scintigraphy and exercise radionuclide ventriculography for distinguishing high- and low-risk patients soon after acute myocardial infarction. *Am J Cardiol.* 1984;53:1221-1227.
586. Abraham RD, Freedman SB, Dunn RF, et al. Prediction of multivessel coronary artery disease and prognosis early after acute myocardial infarction by exercise electrocardiography and thallium-201 myocardial perfusion scanning. *Am J Cardiol.* 1986;58:423-427.
587. Wilson WW, Gibson RS, Nygaard TW, et al. Acute myocardial infarction associated with single vessel coronary artery disease: an analysis of clinical outcome and the prognostic importance of vessel patency and residual ischemic myocardium. *J Am Coll Cardiol.* 1988;11:223-234.
588. Leppo JA, O'Brien J, Rothandler JA, Getchell JD, Lee VW. Dipyridamole-thallium-201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. *N Engl J Med.* 1984;310:1014-1018.
589. Pirelli S, Inglese E, Suppa M, Corradi E, Campolo L. Dipyridamole-thallium-201 scintigraphy in the early post-infarction period: safety and accuracy in predicting the extent of coronary disease and future recurrence of angina in patients suffering from their first myocardial infarction. *Eur Heart J.* 1988;9:1324-1331.
590. Younis LT, Byers S, Shaw L, Barth G, Goodgold H, Chaitman BR. Prognostic value of intravenous dipyridamole thallium scintigraphy after an acute myocardial ischemic event. *Am J Cardiol.* 1989;64:161-166.
591. Figueiredo V, Cheitlin MD. Risk stratification. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction.* London, England: WB Saunders Co Ltd; 1994:361-391.
592. Tilkmeyer PL, Guiney TE, LaRaia PJ, Boucher CA. Prognostic value of predischarge low-level exercise thallium testing after thrombolytic treatment of acute myocardial infarction. *Am J Cardiol.* 1990;66:1203-1207.
593. Hendel RC, Gore JM, Alpert JS, Leppo JA. Prognosis following interventional therapy for acute myocardial infarction: utility of dipyridamole thallium scintigraphy. *Cardiology.* 1991;79:73-80.
594. Miller TD, Gersh BJ, Christian TF, Bailey KR, Gibbons RJ. Limited prognostic value of thallium-201 exercise treadmill testing early after myocardial infarction in patients treated with thrombolysis. *Am Heart J.* 1995;130:259-266.
595. Mahmarian JJ, Mahmarian AC, Marks GF, Pratt CM, Verani MS. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. *J Am Coll Cardiol.* 1995;25:1333-1340.
596. Cerqueira MD, Maynard C, Ritchie JL, Davis KB, Kennedy JW. Long-term survival in 618 patients from the Western Washington Streptokinase in Myocardial Infarction trials. *J Am Coll Cardiol.* 1992;20:1452-1459.
597. Miller TD, Christian TF, Hopfenspirger MR, Hodge DO, Gersh BJ, Gibbons RJ. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. *Circulation.* 1995;92:334-341.
598. O'Keefe JH, Barnhart CS, Bateman TM. Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity. *Am J Cardiol.* 1995;75:25D-34D.
599. Quinones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus 201Tl single-photon emission computed tomography in evaluation of coronary artery disease: analysis of 292 patients. *Circulation.* 1992;85:1026-1031.
600. Marwick TH, Nemec JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting. *J Am Coll Cardiol.* 1992;19:74-81.
601. Armstrong WF, O'Donnell J, Ryan T, Feigenbaum H. Effect of prior myocardial infarction and extent and location of coronary disease on accuracy of exercise echocardiography. *J Am Coll Cardiol.* 1987;10:531-538.
602. Brown KA. Prognostic value of cardiac imaging in patients with known or suspected coronary artery disease: comparison of myocardial perfusion imaging, stress echocardiography, and position emission tomography. *Am J Cardiol.* 1995;75:35D-41D.
603. Hoffman R, Lethen H, Kleinhaus E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. *Am J Cardiol.* 1993;72:555-559.
604. Jaarsma W, Visser CA, Kupper AJ, Res JC, van Eenige MJ, Roos JP. Usefulness of two-dimensional exercise echocardiography shortly after myocardial infarction. *Am J Cardiol.* 1986;57:86-90.
605. Ryan T, Armstrong WF, O'Donnell JA, Feigenbaum H. Risk stratification after acute myocardial infarction by means of exercise two-dimensional echocardiography. *Am Heart J.* 1987;114:1305-1316.
606. Applegate RJ, Dell'Italia LJ, Crawford MH. Usefulness of two-dimensional echocardiography during low-level exercise testing early after uncomplicated acute myocardial infarction. *Am J Cardiol.* 1987;60:10-14.
607. Krivokapich J, Child JS, Gerber RS, Lem V, Moser D. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing twelve months. *Am J Cardiol.* 1993;71:646-651.
608. van Daele ME, McNeill AJ, Fioretti PM, et al. Prognostic value of dipyridamole sestamibi single-photon emission computed tomography and dipyridamole stress echocardiography for new cardiac events after an uncomplicated myocardial infarction. *J Am Soc Echocardiogr.* 1994;7:370-380.
609. Picano E, Mathias WJ, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. *Lancet.* 1994;344:1190-1192.
610. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation.* 1993;87:1-20.
611. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. *Circulation.* 1985;72(suppl V):V-123-V-135.
612. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation.* 1982;66:1146-1149.
613. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med.* 1983;309:331-336.
614. Zaret BL, Wackers FJ, Terrin M, et al. Does left ventricular ejection fraction following thrombolytic therapy have the same prognostic impact described in the prethrombolytic era? Results of the TIMI II Trial. *J Am Coll Cardiol.* 1991;17:214A. Abstract.
615. Roig E, Magrina J, Garcia A, et al. Prognostic value of exercise radionuclide angiography in low risk acute myocardial infarction survivors. *Eur Heart J.* 1993;14:213-218.
616. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation.* 1987;76:44-51.
617. Coleman RE, Klein MS, Roberts R, Sobel BE. Improved detection of myocardial infarction with technetium-99m stannous pyrophosphate and serum MB creatine phosphokinase. *Am J Cardiol.* 1976;37:732-735.
618. Corbett JR, Lewis M, Willerson JT, et al. 99mTc-pyrophosphate imaging in patients with acute myocardial infarction: comparison of planar imaging with single-photon tomography with and without blood pool overlay. *Circulation.* 1984;69:1120-1128.
619. Johnson LL, Seldin DW, Becker LC, et al. Antimyosin imaging in acute transmural myocardial infarctions: results of a multicenter clinical trial. *J Am Coll Cardiol.* 1989;13:27-35.
620. Khaw BA, Gold HK, Yasuda T, et al. Scintigraphic quantification of myocardial necrosis in patients after intravenous injection of myosin-specific antibody. *Circulation.* 1986;74:501-508.
621. Reduto LA, Berger HJ, Cohen LS, Gottschalk A, Zaret BL. Sequential radionuclide assessment of left and right ventricular performance after acute transmural myocardial infarction. *Ann Intern Med.* 1978;89:441-447.
622. Christian TF, Clements IP, Gibbons RJ. Noninvasive identification of myocardium at risk in patients with acute myocardial infarction and nondiagnostic electrocardiograms with technetium-99m-Sestamibi. *Circulation.* 1991;83:1615-1620.
623. Verani MS, Jeroudi MO, Mahmarian JJ, et al. Quantification of myocardial infarction during coronary occlusion and myocardial salvage after reperfusion using cardiac imaging with technetium-99m hexakis 2-methoxyisobutyl isonitrile. *J Am Coll Cardiol.* 1988;12:1573-1581.
624. Sinusas AJ, Trautman KA, Bergin JD, et al. Quantification of area at risk during coronary occlusion and degree of myocardial salvage after reperfusion with technetium-99m methoxyisobutyl isonitrile. *Circulation.* 1990;82:1424-1437.
625. Christian TF, Gibbons RJ, Gersh BJ. Effect of infarct location on myocardial salvage assessed by technetium-99m isonitrile. *J Am Coll Cardiol.* 1991;17:1303-1308.
626. Behrenbeck T, Pellikka PA, Huber KC, Bresnahan JF, Gersh BJ, Gibbons RJ. Primary angioplasty in myocardial infarction: assessment of improved

- myocardial perfusion with technetium-99m isonitrite. *J Am Coll Cardiol.* 1991;17:365-372.
627. Reimer KA, Jennings RB, Cobb FR, et al. Animal models for protecting ischemic myocardium: results of the NHLBI Cooperative Study—comparison of unconscious and conscious dog models. *Circ Res.* 1985;56:651-665.
  628. Corbett JR, Dehmer GJ, Lewis SE, et al. The prognostic value of submaximal exercise testing with radionuclide ventriculography before hospital discharge in patients with recent myocardial infarction. *Circulation.* 1981;64:535-544.
  629. Christian TF, Behrenbeck T, Pellikka PA, Huber KC, Chesebro JH, Gibbons RJ. Mismatch of left ventricular function and infarct size demonstrated by technetium-99m isonitrite imaging after reperfusion therapy for acute myocardial infarction: identification of myocardial stunning and hyperkinesia. *J Am Coll Cardiol.* 1990;16:1632-1638.
  630. Simoons ML, Vos J, Tijssen JG, et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. *J Am Coll Cardiol.* 1989;14:1609-1615.
  631. Hakkı AH, Nestico PF, Heo J, Unwala AA, Iskandrian AS. Relative prognostic value of rest thallium-201 imaging, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring after acute myocardial infarction. *J Am Coll Cardiol.* 1987;10:25-32.
  632. Wackers FJ, Gibbons RJ, Verani MS, et al. Serial quantitative planar technetium-99m isonitrite imaging in acute myocardial infarction: efficacy for noninvasive assessment of thrombolytic therapy. *J Am Coll Cardiol.* 1989;14:861-873.
  633. Gibson WS, Christian TF, Pellikka PA, Behrenbeck T, Gibbons RJ. Serial tomographic imaging with technetium-99m-sestamibi for the assessment of infarct-related arterial patency following reperfusion therapy. *J Nucl Med.* 1992;33:2080-2085.
  634. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation.* 1992;86:81-90.
  635. Gibbons RJ, Verani MS, Behrenbeck T, et al. Feasibility of tomographic 99mTc-hexamis-2-methoxy-2-methylpropyl-isonitrite imaging for the assessment of myocardial area at risk and the effect of treatment in acute myocardial infarction. *Circulation.* 1989;80:1277-1286.
  636. Gottlieb SO, Gottlieb SH, Achuff SC, et al. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. *JAMA.* 1988;259:1030-1035.
  637. Tzivoni D, Gavish A, Zin D, et al. Prognostic significance of ischemic episodes in patients with previous myocardial infarction. *Am J Cardiol.* 1988;62:661-664.
  638. Bonaduce D, Petretta M, Lanzillo T, et al. Prevalence and prognostic significance of silent myocardial ischaemia detected by exercise test and continuous ECG monitoring after acute myocardial infarction. *Eur Heart J.* 1991;12:186-193.
  639. Langer A, Minkowitz J, Dorian P, et al. Pathophysiology and prognostic significance of Holter-detected ST segment depression after myocardial infarction: the Tissue Plasminogen Activator Toronto (TPAT) Study Group. *J Am Coll Cardiol.* 1992;20:1313-1317.
  640. Petretta M, Bonaduce D, Bianchi V, et al. Characterization and prognostic significance of silent myocardial ischemia on predischarge electrocardiographic monitoring in unselected patients with myocardial infarction. *Am J Cardiol.* 1992;69:579-583.
  641. Jereczek M, Andresen D, Schroder J, et al. Prognostic value of ischemia during Holter monitoring and exercise testing after acute myocardial infarction. *Am J Cardiol.* 1993;72:8-13.
  642. Currie P, Ashby D, Saltissi S. Prognostic significance of transient myocardial ischemia on ambulatory monitoring after acute myocardial infarction. *Am J Cardiol.* 1993;71:773-777.
  643. Gill FB, Cairns JA, Roberts RS, et al. Prognostic importance of myocardial ischemia detected by ambulatory monitoring early after acute myocardial infarction. *N Engl J Med.* 1996;334:65-70.
  644. Deedwania PC. Asymptomatic ischemia during predischarge Holter monitoring predicts poor prognosis in the postinfarction period. *Am J Cardiol.* 1993;71:859-861.
  645. Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S. Ventricular premature beats and mortality after myocardial infarction. *N Engl J Med.* 1977;297:750-757.
  646. Moss AJ, Davis HT, DeCamilla J, Bayer LW. Ventricular ectopic beats and their relation to sudden and nonsudden cardiac death after myocardial infarction. *Circulation.* 1979;60:998-1003.
  647. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Roenitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation.* 1984;69:250-258.
  648. Mukharji J, Rude RE, Poole WK, et al. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol.* 1984;54:31-36.
  649. Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *J Am Coll Cardiol.* 1987;10:231-242.
  650. McClements BM, Adey AA. Value of signal-averaged electrocardiography, radionuclide ventriculography, Holter monitoring and clinical variables for prediction of arrhythmic events in survivors of acute myocardial infarction in the thrombolytic era. *J Am Coll Cardiol.* 1993;21:1419-1427.
  651. Hohnloser SH, Franck P, Klingenberg T, Zabel M, Just H. Open infarct artery, late potentials, and other prognostic factors in patients after acute myocardial infarction in the thrombolytic era: a prospective trial. *Circulation.* 1994;90:1747-1756.
  652. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol.* 1991;18:687-697.
  653. Califf RM, Topol EJ, Van der Werf F, Lee KL, Woodlief L, for the GUSTO Investigators. One year followup from the GUSTO I Trial. *Circulation.* 1994;90(suppl I):I-325. Abstract.
  654. Richards DA, Byth K, Ross DL, Uther JB. What is the best predictor of spontaneous ventricular tachycardia and sudden death after myocardial infarction? *Circulation.* 1991;83:756-763.
  655. Kuchar DL, Thorburn CW, Sammel NL. Prediction of serious arrhythmic events after myocardial infarction: signal-averaged electrocardiogram, Holter monitoring and radionuclide ventriculography. *J Am Coll Cardiol.* 1987;9:531-538.
  656. Gomes JA, Winters SL, Martinson M, Machac J, Stewart D, Targonski A. The prognostic significance of quantitative signal-averaged variables relative to clinical variables, site of myocardial infarction, ejection fraction and ventricular premature beats: a prospective study. *J Am Coll Cardiol.* 1989;13:377-384.
  657. El-Sherif N, Denes P, Katz R, et al. Definition of the best prediction criteria of the time domain signal-averaged electrocardiogram for serious arrhythmic events in the postinfarction period: the Cardiac Arrhythmia Suppression Trial/Signal-Averaged Electrocardiogram (CAST/SAECG) Substudy Investigators. *J Am Coll Cardiol.* 1995;25:908-914.
  658. Vatterott PJ, Hammill SC, Bailey KR, Wiltgen CM, Gersh BJ. Late potentials on signal-averaged electrocardiograms and patency of the infarct-related artery in survivors of acute myocardial infarction. *J Am Coll Cardiol.* 1991;17:330-337.
  659. Bigger JT, Fleiss JL, Roenitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation.* 1993;88:927-934.
  660. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* 1987;59:256-262.
  661. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* 1996;93:1043-1065.
  662. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death: experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation.* 1992;85(suppl I):I-77-I-91.
  663. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death: new insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation.* 1988;78:969-979.
  664. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction: a prospective study. *Circulation.* 1988;78:816-824.
  665. Farrell TG, Paul V, Cripps TR, et al. Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. *Circulation.* 1991;83:945-952.

666. Gilman JK, Jalal S, Naccarelli GV. Predicting and preventing sudden death from cardiac causes. *Circulation*. 1994;90:1083-1092.
667. Neuhaus KL, von Essen R, Tebbe U, et al. Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: results of the rt-PA-APSAC patency study (TAPS). *J Am Coll Cardiol*. 1992;19:885-891.
668. Lange RA, Cigarroa RG, Hillis LD. Influence of residual antegrade coronary blood flow on survival after myocardial infarction in patients with multivessel coronary artery disease. *Coronary Artery Dis*. 1990;1:59-63.
669. Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. *Am J Cardiol*. 1989;64:155-160.
670. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction: results of the Survival and Ventricular Enlargement trial—SAVE Investigators. *Circulation*. 1994;90:1731-1738.
671. Ellis SG, da Silva ER, Heyndrickx G, et al. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. *Circulation*. 1994;90:2280-2284.
672. Califf RM, O'Neil W, Stack RS, et al. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. *Ann Intern Med*. 1988;108:658-662.
673. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI II A results. *JAMA*. 1988;260:2849-2858.
674. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med*. 1987;317:581-588.
675. Califf RM, Topol EJ, Stack RS, et al. Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction: results of thrombolysis and angioplasty in myocardial infarction—phase 5 randomized trial. TAMI Study Group. *Circulation*. 1991;83:1543-1556.
676. Jeremy RW, Hackworthy RA, Bautovich G, Hutton BF, Harris PJ. Infarct artery perfusion and changes in left ventricular volume in the month after acute myocardial infarction. *J Am Coll Cardiol*. 1987;9:989-995.
677. Kershaw IE, Brugada P, Ramentol M, et al. Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation: a prospective, randomized study. *J Am Coll Cardiol*. 1986;7:1234-1242.
678. Stadius ML, Davis K, Maynard C, Ritchie JL, Kennedy JW. Risk stratification for 1 year survival based on characteristics identified in the early hours of acute myocardial infarction: the Western Washington Intracoronary Streptokinase Trial. *Circulation*. 1986;74:703-711.
679. Topol EJ, Califf RM, Vandormael M, et al. A randomized trial of late reperfusion therapy for acute myocardial infarction: Thrombolysis and Angioplasty in Myocardial Infarction-6 Study Group. *Circulation*. 1992;85:2090-2099.
680. Dzavik V, Beanlands DS, Davies RF, et al. Effects of late percutaneous transluminal coronary angioplasty of an occluded infarct-related coronary artery on left ventricular function in patients with a recent (<6 weeks) Q-wave acute myocardial infarction (Total Occlusion Post-Myocardial Infarction Intervention Study [TOMIIS]—a pilot study). *Am J Cardiol*. 1994;73:856-861.
681. Simoons ML, Arnold AE, Betriu A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet*. 1988;1:197-203.
682. Duber C, Jungbluth A, Rumpelt HJ, Erbel R, Meyer J, Thoenes W. Morphology of the coronary arteries after combined thrombolysis and percutaneous transluminal coronary angioplasty for acute myocardial infarction. *Am J Cardiol*. 1986;58:698-703.
683. SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. *BMJ*. 1991;302:555-560.
684. Williams DO, Braunwald E, Knatterud G, et al. One-year results of the Thrombolysis in Myocardial Infarction investigation (TIMI) Phase II Trial. *Circulation*. 1992;85:533-542.
685. Terrin ML, Williams DO, Kleiman NS, et al. Two- and three-year results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II clinical trial. *J Am Coll Cardiol*. 1993;22:1763-1772.
686. Barash GI, Roth A, Hod H, et al. Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. *Am J Cardiol*. 1990;66:538-545.
687. Ellis SG, Mooney MR, George BS, et al. Randomized trial of late elective angioplasty versus conservative management for patients with residual stenoses after thrombolytic treatment of myocardial infarction: Treatment of Post-Thrombolytic Stenoses (TOPS) Study Group. *Circulation*. 1992;86:1400-1406.
688. Baim DS, Diver DJ, Feit F, et al. Coronary angioplasty performed within the thrombolysis in Myocardial Infarction II study. *Circulation*. 1992;85:93-105.
689. Chaitman BR, Alderman EL, Sheffield LT, et al. Use of survival analysis to determine the clinical significance of new Q waves after coronary bypass surgery. *Circulation*. 1983;67:302-309.
690. Kugelmas AD, Cohen DJ, Moscucci M, et al. Elevation of the creatine kinase myocardial isoform following otherwise successful directional coronary atherectomy and stenting. *Am J Cardiol*. 1994;74:748-754.
691. Abdelmeguid AE, Whitlow PL, Sapp SK, Ellis SG, Topol EJ. Long-term outcome of transient, uncomplicated in-laboratory coronary artery closure. *Circulation*. 1995;91:2733-2741.
692. Harrington RA, Lincoff AM, Califf RM, et al. Characteristics and consequences of myocardial infarction after percutaneous coronary intervention: insights from the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT). *J Am Coll Cardiol*. 1995;25:1693-1699.
693. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation*. 1994;89:1333-1445.
694. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
695. Sacks FM, Pfeffer MA, Braunwald E, et al, for the CARE Investigators. Effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: preliminary results of the Cholesterol and Recurrent Events (CARE) trial. Presented at the American College of Cardiology Annual Scientific Session; March 1996; Orlando, Fla.
696. Domanski MJ, Huntingake DB, Campeau L. Post CABG trial: effect of cholesterol lowering and low intensity oral anticoagulation on late saphenous vein graft status. Presented at the American College of Cardiology Annual Scientific Session; March 1996; Orlando, Fla.
697. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med*. 1990;322:1700-1707.
698. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA*. 1993;269:3015-3023.
699. Frick MH, Heinonen OP, Huttunen JK, Koskinen P, Manttari M, Manninen V. Efficacy of gemfibrozil in dyslipidaemic subjects with suspected heart disease: an ancillary study in the Helsinki Heart Study Frame population. *Ann Med*. 1993;25:41-45.
700. Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation as Secondary Prevention: Clinical Practice Guideline. Quick Reference Guide for Clinicians*, No. 17. Rockville, Md: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute; October 1995. AHCPR publication 96-0673.
701. Paunio M, Heinonen OP, Virtamo J, et al. HDL cholesterol and mortality in Finnish men with special reference to alcohol intake. *Circulation*. 1994;90:2909-2918.
702. Sagiv M, Goldbourt U. Influence of physical work on high density lipoprotein cholesterol: implications for the risk of coronary heart disease. *Int J Sport Med*. 1994;15:261-266.
703. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med*. 1993;329:1829-1834.
704. Winniford MD, Jansen DE, Reynolds GA, Apprill P, Black WH, Hillis LD.

- Cigarette smoking-induced coronary vasoconstriction in atherosclerotic coronary artery disease and prevention by calcium antagonists and nitroglycerin. *Am J Cardiol.* 1987;59:203-207.
705. Deanfield J, Wright C, Krikler S, Ribeiro P, Fox K. Cigarette smoking and the treatment of angina with propranolol, atenolol, and nifedipine. *N Engl J Med.* 1984;310:951-954.
706. Barry J, Mead K, Nabel EG, et al. Effect of smoking on the activity of ischemic heart disease. *JAMA.* 1989;261:398-402.
707. Burling TA, Singleton EG, Bigelow GE, Baile WF, Gottlieb SH. Smoking following myocardial infarction: a critical review of the literature. *Health Psychol.* 1984;3:83-96.
708. Houston-Miller N, Taylor CB. *Lifestyle Management for Patients With Coronary Heart Disease.* Champaign, Ill: Human Kinetics; 1995.
709. Gourlay SG, McNeil JJ. Antismoking products. *Med J Aust.* 1990;153:699-707.
710. Covey LS, Glassman AH. A meta-analysis of double-blind placebo-controlled trials of clonidine for smoking cessation. *Br J Addict.* 1991;86: 991-998.
711. Bernstein DA. Modification of smoking behavior: an evaluative review. *Psychol Bull.* 1969;71:418-440.
712. Davison GC, Rosen RC. Lobeline and reduction of cigarette smoking. *Psychol Rep.* 1972;31:443-456.
713. Ford SJ, Ederer F. Breaking the cigarette habit. *JAMA.* 1965;194:139-142.
714. Becker RC. Antiplatelet therapy in coronary heart disease: emerging strategies for the treatment and prevention of acute myocardial infarction. *Arch Pathol Lab Med.* 1993;117:89-96.
715. Juul-Møller S, Edvardsson N, Jahnnatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris: the Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet.* 1992;340:1421-1425.
716. Secondary prevention of vascular disease by prolonged antiplatelet treatment: Antiplatelet Trialists' Collaboration. *Br Med J (Clin Res).* 1988;296: 320-331.
717. Collaborative overview of randomised trials of antiplatelet therapy. II: maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ.* 1994;308:159-168.
718. Johnston CI. Franz Volhard Lecture—Renin-angiotensin system: a dual tissue and hormonal system for cardiovascular control. *J Hypertens Suppl.* 1992;10:S13-S26.
719. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril. *Circulation.* 1985;72:406-412.
720. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial—the SAVE Investigators. *N Engl J Med.* 1992;327:669-677.
721. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet.* 1993;342:821-828.
722. Lastini R, Maggioni AP, Flather M, Sleight P, Tognoni G. ACE-inhibitor use in patients with myocardial infarction: summary of evidence from clinical trials. *Circulation.* 1995;92:3132-3137.
723. Johnstone D, Limacher M, Rousseau M, et al. Clinical characteristics of patients in studies of left ventricular dysfunction (SOLVD). *Am J Cardiol.* 1992;70:894-900.
724. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992;327:685-691.
725. Cambien F, Poirier O, Lecerf L, et al. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature.* 1992;359:641-644.
726. Danser AH, Schalekamp MA, Bax WA, et al. Angiotensin-converting enzyme in the human heart: effect of the deletion/insertion polymorphism. *Circulation.* 1995;92:1387-1388.
727. The beta-blocker heart attack trial: Beta-Blocker Heart Attack Study Group. *JAMA.* 1981;246:2073-2074.
728. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med.* 1981;304:801-807.
729. Hjalmarsen A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metopro-  
lol in acute myocardial infarction: a double-blind randomised trial. *Lancet.* 1981;2:823-827.
730. Pedersen TR. Six-year follow-up of the Norwegian Multicenter Study on Timolol after Acute Myocardial Infarction. *N Engl J Med.* 1985;313:1055-1058.
731. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med.* 1993;328:1450-1456.
732. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med.* 1993;328:1444-1449.
733. Gey KF, Puska P, Jordan P, Moser UK. Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology. *Am J Clin Nutr.* 1991;53:326S-334S.
734. Stephens NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet.* 1996;347:781-786.
735. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med.* 1996;334:1156-1162.
736. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med.* 1994;330:1029-1035.
737. Omenn GS, Goodman GE, Thorquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med.* 1996;334:1150-1155.
738. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med.* 1996;334:1145-1149.
739. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology.* 1992;3:194-202.
740. Flaherty JT, Pitt B, Gruber JW, et al. Recombinant human superoxide dismutase (h-SOD) fails to improve recovery of ventricular function in patients undergoing coronary angioplasty for acute myocardial infarction. *Circulation.* 1994;89:1982-1991.
741. DeMaio SJ, King SB, Lembo NJ, et al. Vitamin E supplementation, plasma lipids and incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA). *J Am Coll Nutr.* 1992;11:68-73.
742. Leaf A, Jorgensen MB, Jacobs AK, et al. Do fish oils prevent restenosis after coronary angioplasty? *Circulation.* 1994;90:2248-2257.
743. ASPECT Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction: anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. *Lancet.* 1994;343:499-503.
744. Cairns JA, Markham BA. Economics and efficacy in choosing oral anticoagulants or aspirin after myocardial infarction. *JAMA.* 1995;273: 965-967.
745. Fuster V. Low-dose coumadin plus low-dose aspirin following myocardial infarction (CARS Trial). Presented at the American College of Cardiology Scientific Session; March 1996; Orlando, Fla.
746. Weintraub WS, Ba'albaki HA. Decision analysis concerning the application of echocardiography to the diagnosis and treatment of mural thrombi after anterior wall acute myocardial infarction. *Am J Cardiol.* 1989;64:708-716.
747. Hansen JF. Treatment with verapamil after an acute myocardial infarction: review of the Danish studies on verapamil in myocardial infarction (DAVIT I and II). *Drugs.* 1991;42(suppl 2):43-53.
748. Rafflenbeul W, Ebner F. Myocardial infarction: secondary prevention with nifedipine. *Drugs.* 1991;42(suppl 2):38-42.
749. Frishman WH, Skolnick AE, Miller KP. Secondary prevention post infarction: the role of  $\beta$ -adrenergic blockers, calcium channel blockers, and aspirin. In: Gersh BJ, Rahimtoola SH, eds. *Acute Myocardial Infarction.* New York, NY: Elsevier Science Publishing Co; 1990:469-492.
750. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. *Am J Cardiol.* 1991;67:1295-1297.
751. Hansen JF. Secondary prevention with calcium antagonists after a myocardial infarction. *Arch Intern Med.* 1993;153:2281-2282.
752. The Danish Study Group on Verapamil in Myocardial Infarction. Secondary prevention with verapamil after myocardial infarction. *Am J Cardiol.* 1990;66(suppl):331-401.

753. Kloner RA. Nifedipine in ischemic heart disease. *Circulation*. 1995;92:1074-1078.
754. Yusuf S. Calcium antagonists in coronary artery disease and hypertension: time for reevaluation? *Circulation*. 1995;92:1079-1082.
755. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA*. 1995;274:620-625.
756. Stevenson JC, Crook D, Godsland IF, Collins P, Whitehead MI. Hormone replacement therapy and the cardiovascular system: nonlipid effects. *Drugs*. 1994;47(suppl 2):35-41.
757. Kafonek SD. Postmenopausal hormone replacement therapy and cardiovascular risk reduction: a review. *Drugs*. 1994;47(suppl 2):16-24.
758. Petitti DB. Coronary heart disease and estrogen replacement therapy: can compliance bias explain the results of observational studies? *Ann Epidemiol*. 1994;4:115-118.
759. Healy B. Effects of estrogen or estrogen/progestin regimes on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1995;273:199-208.
760. Whitehead M. Progestins and androgens. *Fertil Steril*. 1994;62(suppl 2):161S-167S.
761. Lobo RA, Speroff L. International consensus conference on postmenopausal hormone therapy and the cardiovascular system. *Fertil Steril*. 1994;61:592-595.
762. Stanford JL, Weiss NS, Voight LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. *JAMA*. 1995;274:137-142.
763. Colditz GA, Hankinson SE, Hunter DJ, Willett WC. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med*. 1995;332:1589-1593.
764. Gorsky RD, Koplan JP, Peterson HB, Thacker SB. Relative risks and benefits of long-term estrogen replacement therapy: a decision analysis. *Obstet Gynecol*. 1994;83:161-166.
765. Guidelines for counseling postmenopausal women about preventive hormone therapy: American College of Physicians. *Ann Intern Med*. 1992;117:1038-1041.
766. Burkart F, Pfisterer M, Kiowski W, Follath F, Burckhardt D. Effect of antiarrhythmic therapy on mortality in survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias: Basel Antiarrhythmic Study of Infarct Survival (BASIS). *J Am Coll Cardiol*. 1990;16:1711-1718.
767. Ceremuzynski L, Kleczar E, Krzeminska-Pakula M, et al. Effect of amiodarone on mortality after myocardial infarction: a double-blind, placebo-controlled, pilot study. *J Am Coll Cardiol*. 1992;20:1056-1062.
768. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia: Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med*. 1995;333:77-82.
769. Leon AS, Certo C, Comoss P, et al. Scientific evidence of the value of cardiac rehabilitation services with emphasis on patients following myocardial infarction. *J Cardiopulmonary Rehabil*. 1990;10:79-87.
770. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. *JAMA*. 1988;260:945-950.
771. Myers J, Ahnve S, Froelicher V, et al. A randomized trial of the effects of 1 year of exercise training on computer-measured ST segment displacement in patients with coronary artery disease. *J Am Coll Cardiol*. 1984;4:1094-1102.
772. Schuler G, Hambrecht R, Schlierf G, et al. Myocardial perfusion and regression of coronary artery disease in patients on a regimen of intensive physical exercise and low fat diet. *J Am Coll Cardiol*. 1992;19:34-42.
773. Fletcher GF, Blair SN, Blumenthal J, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1992;86:340-344.
774. Shaw RE, Cohen F, Doyle B, Palesky J. The impact of denial and repressive style on information gain and rehabilitation outcomes in myocardial infarction patients. *Psychosom Med*. 1985;47:262-273.
775. Cardiac rehabilitation programs: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1994;90:1602-1610.
776. DeBusk RF, Miller NH, Superko HR, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med*. 1994;120:721-729.
777. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am J Epidemiol*. 1979;109:186-204.
778. Case RB, Moss AJ, Case N, McDermott M, Eberly S. Living alone after myocardial infarction: impact on prognosis. *JAMA*. 1992;267:515-519.
779. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. *N Engl J Med*. 1984;311:552-559.
780. Riegel BJ, Dracup KA. Does overprotection cause cardiac invalidism after acute myocardial infarction? *Heart Lung*. 1992;21:529-535.
781. Coppotelli HC, Orleans CT. Partner support and other determinants of smoking cessation maintenance among women. *J Consult Clin Psychol*. 1985;53:455-460.
782. Hodgson TA. Health care expenditures for major diseases in 1980. *Heart Care Financing Review*. 1984;5.
783. Rost K, Smith GR. Return to work after an initial myocardial infarction and subsequent emotional distress. *Arch Intern Med*. 1992;152:381-385.
784. Froelicher ES, Kee LL, Newton KM, Lindskog B, Livingston M. Return to work, sexual activity, and other activities after acute myocardial infarction. *Heart Lung*. 1994;23:423-435.
785. Brodie B, Grines CL, Spain M, et al. A prospective, randomized trial evaluating early discharge (day 3) without non-invasive risk stratification in low risk patients with acute myocardial infarction: PAMI-2. *J Am Coll Cardiol*. 1995;25:S.A. Abstract.
786. Usher MC, Dennis CA, Schwartz RG, Ahn DK, DeBusk RF. Physician influences on timing of return to work after myocardial infarction. *Circulation*. 1986;74(suppl II):II-490. Abstract.
787. US Department of Transportation. *Status of Medical Review in Driver Licensing: Policies, Programs and Standards*. 1992.

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## ACC/AHA PRACTICE GUIDELINES

# 1999 Update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction

A Report of the American College of Cardiology/  
American Heart Association Task Force on Practice  
Guidelines (Committee on Management of Acute Myocardial Infarction)

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The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients With Acute Myocardial Infarction have been

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reviewed over the past 2½ years since their initial publication (*J Am Coll Cardiol* 1996;28:1328-428) to ensure their continued relevancy. The guidelines have been updated to include the most significant advances that have occurred in the management of patients with acute myocardial infarction (AMI) during that time frame. This Update was developed to keep the guidelines current without republishing them in their entirety. The Update represents a new procedure of the ACC/AHA Task Force on Practice Guidelines. These guidelines will be reviewed and updated as necessary until it is deemed appropriate to revise and republish the entire document.

This Update, as printed here in the *Journal of the American College of Cardiology*, appears without the full text guidelines. The full text guidelines, incorporating the Update, are available on the Web sites of both the American College of Cardiology ([www.acc.org](http://www.acc.org)) and the American Heart Association ([www.americanheart.org](http://www.americanheart.org)). In the Web site version, deleted text is indicated by ~~XXXXXXXXXX~~, and new/revised text is presented in a highlighted typeface. Reprints of the original 1996 document with the revised sections appended are available from both organizations (see footnote).

This Update is presented in 4 sections as follows:

1. Changes/additions to text
2. New and revised figures and tables
3. Changes in Class I, II, and III recommendations
4. Changes in references

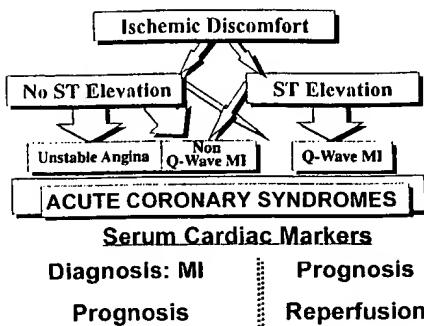
This Update to the guidelines represents a new procedure. Comments about this approach and format are encouraged and should be sent to Chair, ACC/AHA Task Force on Practice Guidelines, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814.

*New section, page 1340, column 2: new text replaces paragraphs beginning "An ideal serum marker . . ." through page 1342, column 1, "Assays for biochemical . . ."*

**Serum cardiac markers.** When myocytes become necrotic, they lose membrane integrity, and intracellular macromolecules diffuse into the cardiac interstitium and ultimately into the cardiac microvasculature and lymphatics (55). Eventually, these macromolecules are detectable in the peripheral circulation. The term currently used to collectively describe these macromolecules is serum cardiac markers. An ideal serum cardiac marker of MI should be present early and in high concentration in the myocardium and should be absent from nonmyocardial tissue and serum (55–57). It should be rapidly released into the blood at the time of the myocardial injury, and there should be a stoichiometric relation between the plasma level and the extent of myocardial injury. The marker should persist in blood for a sufficient length of time to provide a convenient diagnostic time window. Finally, measurement of the marker should be easy, inexpensive, and rapid.

The nomenclature of the acute coronary syndromes (ACS) is illustrated in revised Figure 2. The central position of the 12-lead electrocardiogram (ECG) and initial triage of patients are emphasized. Listed at the bottom of the figure is the information sought by clinicians when measuring serum cardiac marker levels in patients at different ends of the ACS spectrum. Serum cardiac markers are useful for confirming the diagnosis of MI when patients present without ST-segment elevation, when the diagnosis may be unclear, and when clinicians must distinguish patients with unstable angina from those with a non-Q-wave MI. Serum cardiac markers also provide valuable prognostic information. For patients with ST-segment elevation, the diagnosis of MI is secure; clinicians are interested in prognostic information as well as a noninvasive assessment of the likelihood that the patient has undergone successful reperfusion when thrombolytic therapy is administered.

Because the conventional serum cardiac marker, creatine kinase (CK) and its MB isoenzyme (CK-MB) lack sufficient sensitivity and specificity, there is a need for more sensitive and cardiac-specific markers of myocardial necrosis (792–794). The troponin complex consists of 3 subunits: troponin T, troponin I, and troponin C (795). The ternary troponin complex is a calcium-sensitive molecular apparatus that



**Figure 2.** Patients with ischemic discomfort may present with or without ST-segment elevation on the electrocardiogram. The majority (large arrow) of patients with ST-segment elevation ultimately develop a Q-wave AMI, whereas a minority (small arrow) develop a non-Q-wave AMI. Of patients who present without ST-segment elevation, the majority (large arrows) are ultimately diagnosed as having either unstable angina or non-Q-wave AMI based on the presence or absence of a cardiac marker such as CK-MB detected in the serum; a minority of such patients ultimately develop a Q-wave AMI. The spectrum of clinical conditions ranging from unstable angina to non-Q-wave AMI and Q-wave AMI is referred to as acute coronary syndromes. AMI = acute myocardial infarction.

Adapted from Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald EB, editor. Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia, PA: WB Saunders; 1996.

regulates the interaction of actin and myosin. Troponin T binds the troponin complex to tropomyosin, and troponin I binds to actin and inhibits interactions between actin and myosin. Troponin C is responsive to changes in intracellular calcium concentration. Amino acid sequences of the skeletal and cardiac isoforms of troponin I and troponin T have sufficient dissimilarity that monoclonal antibody-based immunoassays have been developed to detect cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI). Because the amino acid sequence of troponin C is the same in cardiac and skeletal muscle, no immunoassays of troponin C have been developed for clinical purposes.

Because CK-MB is found in the skeletal muscle and blood of healthy subjects, the cutoff value for an elevated CK-MB level is typically set a few units above the upper end of the reference (normal) range. In contrast, because cardiac troponin I and cardiac troponin T are not normally detected in the blood of healthy people, the cutoff value for elevated cTnI and cTnT levels may be set only slightly above the noise level of the assay, permitting clinicians to diagnose lesser degrees of myocardial necrosis (ie, increased sensitivity) (796). Because CK and CK-MB are characteristically used as the gold standard for diagnosing MI, investigators may face a dilemma when a new diagnostic test is more sensitive than the gold standard, particularly for identifying episodes of minor myocardial cell necrosis. Case reports confirm histologic evidence of focal myocyte necrosis in patients with elevated cardiac troponin levels and normal

CK values (796). It is estimated that ≈30% of patients presenting without ST-segment elevation who would otherwise be diagnosed with unstable angina are actually experiencing a non-Q-wave MI when assessed with cardiac-specific troponin assays (797). Furthermore, numerous investigators have now reported that elevated levels of cTnI or cTnT provide more prognostic information than that supplied by the patient's demographic characteristics or the ECG at presentation (798,799). Elevated cTnI or cTnT levels, even in the presence of normal CK-MB levels, identify patients without ST-segment elevation who are at an increased risk of death. Finally, patients presenting without ST-segment elevation who are characterized as high risk because of elevated cardiac-specific troponin levels demonstrate a greater benefit from treatment with new therapies such as glycoprotein (GP) IIb/IIIa inhibitors than patients without elevated cardiac-specific troponin levels who receive such new pharmacotherapeutic interventions (800).

CK-MB isoforms are another new serum cardiac marker that may be useful for evaluating patients with an acute coronary syndrome. CK-MB exists in only 1 form in myocardial tissue but in different isoforms (or subforms) in the plasma. An absolute level of CK-MB<sub>2</sub> >1 U/L or a ratio of CK-MB<sub>2</sub> to CK-MB<sub>1</sub> of 1.5 has improved sensitivity and specificity for diagnosis of MI within the first 6 hours compared with conventional assays for CK-MB (59). Myoglobin, a low-molecular-weight heme protein found in cardiac and skeletal muscle, is not cardiac specific but is released more rapidly from infarcted myocardium than CK-MB and may be detected as early as 2 hours after MI. The diagnostic sensitivity and specificity for MI were compared for total CK-MB (activity and mass), CK-MB subforms, myoglobin, cTnI, and cTnT in the Diagnostic Marker Cooperative Study (DMCS) (801). The DMCS was a large, prospective, multicenter, double-blind study of patients presenting in the emergency department (ED) with chest pain. CK-MB subforms were most efficient for early diagnosis (within 6 hours) of MI, whereas cTnI and cTnT were highly cardiac specific and particularly efficient for late diagnosis of MI. The DMCS investigators concluded that either a single assay (CK-MB subforms) or a select combination (CK-MB subform and a cardiac-specific troponin) reliably triages patients with chest pain and could potentially lead to improved therapy and reduced cost of care of ACS patients. It should be noted that serum levels of cTnT and cTnI may be present for several days after MI (up to 7 days for cTnI and up to 10 to 14 days for cTnT). Therefore, the ability to diagnose recurrent infarction is significantly compromised if the clinician relies solely on cardiac-specific troponins and fails to obtain a concomitant CK or CK-MB measurement within the first 12 to 24 hours of admission of an MI patient. Thus, although CK and CK-MB are not as cardiac specific as the troponins, they will return to normal levels within the first 24 to 36 hours, making it more likely that a reelevation is associated with recurrent myocardial

necrosis. For patients presenting within the first 2 or 3 hours of symptom onset, the 2 markers most appropriate for the early diagnosis of AMI are myoglobin and CK-MB subforms.

In patients presenting with ST-segment elevation, clinicians usually use peak CK as a rough estimate of the magnitude of the infarct and assessment of the patient's prognosis. Release of cardiac-specific troponins is stoichiometrically correlated with the amount of myocardial necrosis, and the new serum cardiac markers can also be used to estimate infarct size and prognosis (58). Cardiac-specific troponins may not be detectable for up to 6 hours after onset of chest pain. Thus, when cTnI and cTnT levels are elevated early after onset of discomfort in patients with ST-segment elevation MI, clinicians should suspect that an antecedent episode of unstable angina was in fact MI and the patient is exhibiting a stuttering course of occlusion and release of the infarct-related artery. Data from the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) III Study suggest that patients with elevated cardiac troponin T levels and who are <6 hours from the onset of discomfort have an increased mortality risk (802).

In addition to monitoring the patient for resolution of ischemic-type chest discomfort and regression of the magnitude of ST-segment elevation on the ECG, clinicians can obtain serial measurements of serum cardiac markers to buttress the noninvasive diagnosis of reperfusion of the infarct-related artery after thrombolytic therapy (65,803). Because of its rapid-release kinetics, myoglobin is a particularly attractive marker for the early diagnosis of reperfusion.

*New section: Follows "Serum Cardiac Markers" (see page 1340, column 2)*

**Bedside testing for serum cardiac markers.** Handheld rapid bedside assays are clinically available for measuring cTnI, cTnT, myoglobin, and CK-MB. Small desktop rapid analyzers are also available for the same purpose. A rapid, high-voltage electrophoretic system is available for measuring CK-MB isoforms. When using a handheld rapid bedside assay for a serum cardiac marker, the clinician places a small aliquot of the patient's blood or serum in the specimen well and observes the development of a colored line in the read zone of the device. It should be noted that the time to development of the colored line and the intensity of the color are related to the concentration of the serum cardiac marker in the specimen. For example, when a handheld bedside immunoassay is used to test the blood of patients with high cTnT levels, a red line quickly appears; such patients are at increased mortality risk (804). Careful attention to the timing of the appearance of a positive bedside assay result may provide clinicians with a tool for a semiquantitative estimate of a serum cardiac marker level at the patient's bedside. A positive bedside test, however, should be confirmed by a conventional quantitative test.

**New Table 2.1.** Intracranial Hemorrhage in Recent Thrombolytic Trials

Patient Characteristics	GUSTO-I (497)	GUSTO-II (805)	COBALT (832)	GUSTO-III (802,833)	ASSENT-2*	In Time-II*
Number	41,021	3473	7169	15,059	16,950	15,078
Average age (y)	62	62.5	62.4	63	—	—
>75 y (%)	10.5	11.8	13.0	13.6	—	—
Female (%)	25.2	22.4	23.4	27.4	—	—
Intracranial Hemorrhage Rates						
SK	0.51	0.37	—	—	—	—
tPA	0.70	0.72	Double bolus 1.12 Accl infusion 0.81	0.87	0.93	0.62
rPA	—	—	—	0.91	—	—
TNK-tPA	0.7	0.72	—	—	0.94	—
nPA	—	—	—	—	—	1.13

accl = accelerated, nPA = lanetoplasin, rPA = reteplase, TNK-tPA = a genetically engineered variant of tPA, tPA = tissue plasminogen activator, SK = streptokinase.

\*Data based on preliminary results.

***Text added to "Risk of Stroke," page 1348, column 1: new text added after paragraph beginning "Thrombolytic therapy is associated with..."***

More recent trials show that as use of thrombolysis has increased, a greater proportion of patients who are >75 years old or female are now included. This change has been associated with a higher rate of intracranial hemorrhage (ICH) than that seen in earlier studies. For example, the rate of ICH after administration of alteplase was ≈0.7%; in more recent studies, it is 0.8 to 0.9% (new Table 2.1). It should be noted that the streptokinase without heparin administration regimen has the lowest rate of ICH.

***Text added to "Primary Percutaneous Transluminal Coronary Angioplasty," page 1351, column 1: new text replaces paragraph beginning "A meta-analysis suggests..."***

In the GUSTO-IIb trial (805), 1138 patients with evolving ST-segment elevation MI within 12 hours of onset of chest pain were randomly assigned to receive primary percutaneous transluminal coronary angioplasty (PTCA) ( $n = 565$ ) or accelerated tissue plasminogen activator (tPA) ( $n = 573$ ). Thirty days after enrollment, the incidence of death, recurrent MI, or disabling stroke was 9.6% in those who underwent PTCA and 13.6% in those who received tPA ( $P = 0.033$ ). However, 6 months after enrollment the difference between the 2 treatments did not reach statistical significance; the incidence of the composite adverse outcome was 13.3% in the PTCA group and 15.7% in the tPA group ( $P = NS$ ).

Recently published data from the Second National Registry of Myocardial Infarction (NRMI-2) (124) suggest that primary PTCA and thrombolytic therapy offer similar efficacy. Over 17 months, 4939 subjects with evolving ST-segment elevation MI received primary PTCA, and 24,705 received alteplase. For patients without cardiogenic shock, the in-hospital mortality rate was similar (5.4% for

the alteplase group, 5.2% for the PTCA group), and this was true even when the data from certain "high-risk" subgroups, such as those >75 years old and those with anterior MI, were analyzed.

Among the most important contributions to these revised guidelines are the data in the preliminary report of the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) Trial, presented by Dr Judith Hochman on March 7, 1999, at the 48th Scientific Sessions of the American College of Cardiology, held in New Orleans, Louisiana and to be published in the August 26, 1999 issue of the *New Engl J Med* (805a). When this multicenter study was designed in 1992, it was postulated that emergency revascularization (ERV) of cardiogenic shock due to an ST-elevation/Q-wave or new left bundle-branch block (LBBB) MI would result in a 20% (absolute) reduction in the primary end point, all-cause 30-day mortality compared with initial medical stabilization (IMS), and delayed revascularization as clinically determined.

In this study, 152 patients were randomly assigned to the ERV strategy, and 150 patients were assigned to a strategy of IMS. The 30-day mortality rate for ERV patients was 46.7% versus 56.0% for IMS patients (95% confidence interval [CI], -20.5 to +1.9%,  $P = 0.11$ ), a nonsignificant trend. However, the mortality rate at 6 months (a secondary end point) was significantly lower in the ERV group (50.3% versus 63.1%,  $P = 0.27$ ). The prespecified subgroup analysis of patients <75 years old showed a 15.4% reduction in the primary end point (IMS group, 56.8%, versus ERV group, 41.4%,  $P < 0.01$ ), whereas outcome in patients >75 years old was worse for the ERV group. Intra-aortic balloon pump (IABP) support was used in 86% of both groups; 63% of the IMS group received thrombolytic agents, and 25% underwent delayed revascularization. Of the ERV group of patients who underwent emergency early revascularization, ≈60% received PTCA, and 40% had coronary artery bypass graft (CABG); the 30-day mortality rate was 45% and 42%, respectively.

An early meta-analysis of the randomized clinical trials that compared primary PTCA with thrombolytic therapy was reported in early 1995 (121) and included data on in-hospital or 6-week mortality and nonfatal MI for all 7 trials reported to that time. The combined data showed a mortality rate at 6 weeks of 3.7% in the PTCA group and 6.4% in the thrombolysis group (odds ratio [OR], 0.56; 95% CI, 0.33 to 0.94). In the combined outcome of short-term mortality and nonfatal reinfarction, the event rate was 6.1% for the PTCA group and 11.0% for the thrombolytic therapy group (OR, 0.53; 95% CI, 0.35 to 0.80). By 1 year, however, none of these end point differences were statistically significant. The analyses showed that ≈30% of the thrombolytic therapy patients underwent PTCA sometime during hospitalization or within the first 6 weeks of infarction. Therefore, the contrast in the proportions of patients receiving any PTCA versus patients receiving no PTCA was substantial (64%). The authors conclude that the data on primary PTCA appear promising but should be interpreted with caution and viewed as a strong impetus for the conduct of larger trials in a more diverse range of hospitals, with clinical outcomes being the primary end points of interest.

A more recent meta-analysis by Weaver et al (806) provides a quantitative review of the treatment effects of primary coronary angioplasty versus intravenous thrombolysis for AMI from 10 randomized trials that involved 2606 patients. When the results of all studies were combined, the mortality rate at ≤30 days was 4.4% for the 1290 patients treated with primary angioplasty, compared with 6.5% for the 1316 patients treated with thrombolysis (34% reduction; OR, 0.66%; 95% CI, 0.46 to 0.94;  $P = 0.02$ ). The pooled rate of death or nonfatal reinfarction was also lower in patients treated with primary PTCA than in those treated with thrombolytic therapy, from 11.9% to 7.2%, respectively (OR, 0.58; 95% CI, 0.44 to 0.76). Angioplasty was associated with a significant reduction in total stroke (9/1290, 0.7%; versus 26/1316, 2%;  $P = 0.007$ ) and hemorrhagic strokes as well (0.1% versus 1.1%;  $P < 0.001$ ). On the basis of outcomes at hospital discharge or 30 days, this analysis concluded that "primary PTCA appears to be superior to thrombolytic therapy for treatment of patients with AMI, with the proviso that success rates for PTCA are as good as those achieved in these trials. Data evaluating longer-term outcome, operator expertise, and time delays before treatment are needed before primary PTCA can be recommended universally as the preferred treatment." Recently Brodie et al (788) pointed out that patients who underwent angioplasty within 2 hours of onset of symptoms showed a striking 53% relative reduction in 30-day mortality compared with those who underwent angioplasty >2 to 6 hours (4.3% versus 9.2%;  $P < 0.04$ ). Because their data failed to show an important time-dependent worsening of mortality beyond 2 hours, it has been suggested that the time delay in transferring patients with AMI to tertiary centers for primary PTCA may be permissible if the procedure cannot

be done within the first 2 hours of symptom onset. Clearly, it becomes critical to measure the outcomes of larger numbers of patients stratified by time to answer this important question. On the other hand, if a time-dependent worsening of mortality does exist for patients undergoing angioplasty (as seems likely since it does so for patients reperfused with fibrinolytic therapy), it seems reasonable to explore the theoretical advantage of combining the administration of smaller doses of fibrinolytic agents on presentation at the community hospital (for early patency) with prompt transfer to a tertiary center for percutaneous coronary intervention (PCI) (sustained patency). The safety of such an approach has been reported by Dr. Allan Ross for the PACT Trial at the 71st Scientific Sessions of the American Heart Association, in Dallas, Texas, on November 10, 1998.

Until more data have more reliably quantified a benefit of primary PTCA over thrombolytic therapy in the community setting, it seems prudent to suggest that institutions that do not have the capability of offering primary PTCA should not feel compelled to develop such services at this time (121,807).

*Text added to "Primary PTCA," page 1351, column 2:  
new paragraph added before "Recommendations for Early Coronary Angiography . . ."*

The most recent developments in acute reperfusion by mechanical interventions in the management of patients with AMI are the emerging reports of randomized comparisons between primary PTCA and routine deployment of stents (127,808). The Amsterdam group (127) published a randomized comparison of coronary stenting with balloon angioplasty in selected patients with AMI that showed that primary stenting can be used safely and effectively, resulting in a lower incidence of recurrent infarction and a significant reduction in the need for subsequent target-vessel revascularization compared with balloon angioplasty. These data support the concept that with improved stent technique and use of more effective antiplatelet regimens, including ticlopidine, the thrombus-laden lesion no longer represents a strict contraindication to stenting. An appropriate note of caution has been made about interpreting these data (809), pointing out the highly selective nature of the study population. Only 50% of patients with AMI who underwent primary PTCA were considered eligible for this study, raising serious questions about the generalizability of the results.

The STENT PAMI (Stents—Primary Angioplasty in Acute MI) Trial reported the results of randomly assigning 900 AMI patients to PTCA or PTCA with deployment of a heparin-coated stent at the 71st Scientific Sessions of the American Heart Association held in Dallas in November 1998. The primary end point was the incidence of the combination of death, reinfarction, disabling stroke, or ischemic-driven, target-vessel revascularization at 6 months. Although there was a statistically significant difference in the combined end point that favored stent placement

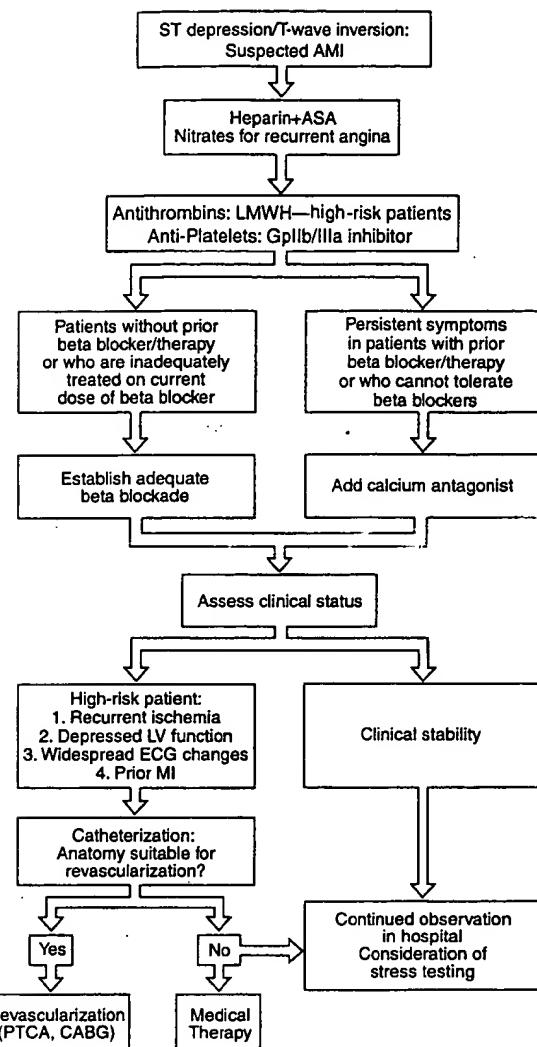
compared with PTCA alone (12.4% versus 20.1%,  $P < 0.01$ ), this was determined solely by the incidence of target-vessel revascularization at 6 months (7.5% versus 17%,  $P < 0.0001$ , respectively). Unfortunately, there were more deaths in the stent placement arm (4.2%) than in the PTCA arm (2.7%), although the difference was not statistically significant in this trial, which had a total of only 31 deaths.

**Text added to "Patient Characteristics," page 1352, column 1: new text replaces paragraphs beginning "Ischemic-type chest discomfort . . ." through "The early descriptions of MI . . ."**

In the setting of nondiagnostic ECG findings (non-ST elevation), ACS represents a continuum between chronic stable angina and AMI with ST-segment elevation. Although the prognosis of the patient with chronic stable angina can be stratified and the emergency situation engendered by ST-elevation MI is readily evident, patients with acute symptoms but nondiagnostic ECG findings range from those with noncardiac chest pain to very high-risk MI with multivessel disease. Unstable angina and MI without ST elevation represent 2 of the most common cardiac emergencies requiring hospitalization and account for >650,000 discharges per year in the United States. Although the optimal treatment regimen or strategies for such patients is under investigation, a proposed diagnostic schema is presented in Figure 2 and a therapeutic approach is depicted in revised Figure 4.

AMI accompanied by nondiagnostic ECG changes is believed to be related to acute disruption of an atherosclerotic plaque in the setting of chronic inflammatory infiltration of its fibrous cap; this underlying pathophysiology is not thought to differ from AMI accompanied by ST-segment elevation. As more angiographic and clinical correlation studies are done, it is becoming clear that total occlusion of the culprit vessel is much less common in AMI without ST-segment elevation than in MI with ST elevation (82,138–140). Furthermore, patients without ST-segment elevation are more likely to have multivessel disease and prior MIs than are those with ST-elevation MI (810). In the clinical history, patients with MI without ST-segment elevation are more likely than those with ST elevation to have a history of diabetes, hypertension, heart failure, and peripheral vascular disease but less likely to be smokers or to have hyperlipidemia (810). Importantly, the elderly are less likely to have ST-segment elevation with MI, probably because of the more common presence of prior myocardial damage and multivessel disease (25,149).

Thus, during initial evaluation of the patient with acute ischemic-type chest discomfort, the clinician should classify patients as those with ST elevation or LBBB (acute reperfusion indicated) and those with nondiagnostic ECGs. The nondiagnostic ECG group will include patients with noncardiac symptoms, those with unstable angina and no myocardial necrosis, those with small MIs, those with direct



**Figure 4.** All patients without ST elevation should be treated with an antithrombin and aspirin (ASA). Nitrates should be administered for recurrent episodes of angina. Adequate  $\beta$ -adrenoceptor blockade should then be established; when this is not possible or contraindications exist, a calcium antagonist can be considered. Current data indicate that either an invasive or noninvasive treatment strategy is suitable for non-ST-elevation AMI patients. AMI = acute myocardial infarction, CABG = coronary artery bypass graft; ECG = electrocardiographic, GpIIb/IIIa = glycoprotein IIb/IIIa receptor for platelet aggregation, LMWH = low-molecular-weight heparin, LV = left ventricular, PTCA = percutaneous transluminal coronary angioplasty.

Modified from Antman EM. Medical therapy for acute coronary syndromes: an overview. In: Calif RM, editor. Atlas of Heart Diseases, VIII. Philadelphia: Current Medicine; 1996.

posterior infarctions caused by circumflex artery occlusion, and those at very high risk with multivessel coronary disease and significant left ventricular dysfunction. Studies with different mixes of these subgroups have reported different morbidity and mortality rates for the population as a whole.

The initial importance of classifying patients on the basis of the ECG should not be confused with the question of whether the patient has a Q-wave or a non-Q-wave MI. This classification can be made only after 24 hours, well beyond the point at which critical decisions about treatment must be made. Whether or not the patient initially has ST elevation, those with a normal QRS complex who do not develop Q waves with MI have a low in-hospital mortality rate, but recurrent ischemia, recurrent MI, and death in the weeks after discharge occur frequently. In contrast, patients with a significant QRS abnormality who do not develop new Q waves with a new MI are at high risk of both early and later death. The overall incidence of non-Q-wave MI may be increasing with the advancing age of the population and the greater use of thrombolytic therapy, aspirin, and  $\beta$ -adrenoreceptor blockers.

*New section, page 1353, column 2: new text added before "Interventional Therapy"*

**Antithrombotic therapy.** Thousands of patients with ACS without ST-segment elevation have now been randomly assigned to treatment with various antithrombotic regimens. In these trials, approximately half the patients had enzymes positive for myocardial necrosis on the first measurement, indicating that they were having an MI without ST-segment elevation at the time of randomization. Patients with positive enzymes on the first draw not only had a higher mortality rate than patients without positive enzymes, but they also had a higher risk of repeat MI, hemodynamic complications, and arrhythmias. Fortunately, the response to newer antithrombotic agents has been homogeneous in patients with ACS without ST elevation, whether or not they had positive enzymes at the time of admission.

*New section, page 1353, column 2: new text added before "Interventional Therapy." Follows "Antithrombotic Therapy."*

**Glycoprotein IIb/IIIa inhibitors.** The GP IIb/IIIa receptor is a member of the integrin family of receptors that is found in the membrane of platelets (811). When platelets are activated by a variety of stimuli, including thrombin, collagen, adenosine diphosphate (ADP), and epinephrine, the GP IIb/IIIa receptor changes conformation to be receptive to one end of a fibrinogen dimer. Occupancy of a GP IIb/IIIa receptor by the other end of the dimer provides the basis for platelet aggregation. Thus, the GP IIb/IIIa receptor is considered the final common pathway of platelet aggregation (812). Multiple therapeutic agents have now been developed to block the receptor.

More than 30,000 patients with ACS without ST-segment elevation have now been randomly assigned into trials comparing GP IIb/IIIa inhibitors with placebo in addition to treatment with aspirin and unfractionated heparin (UFH). A systematic overview has demonstrated a definite reduction in the composite end point of death and MI and in the composite end point of death, MI, and the need for revascularization procedures (813). A slight trend toward a

reduction in mortality may exist but does not reach statistical significance. The reduction in events is present while patients are treated with active drug, and the difference in event rates does not change after that point. When treatment is discontinued, no further effect, either beneficial or detrimental, is seen. Thus, intravenous GP IIb/IIIa inhibitors may be considered as a method to reduce acute events and stabilize patients in the acute phase of MI without ST-segment elevation. Direct comparisons of the agents are not available, so the specific choice of which agent to use is speculative.

Three agents are available for clinical practice:

1. Abciximab is a chimeric Fab fragment of a monoclonal antibody to the GP IIb/IIIa receptor. Although multiple clinical trials have documented the reduction in the composite of death and nonfatal MI with abciximab in the setting of percutaneous intervention (814-817), only 1 trial (Chimeric 7E3 Antiplatelet in Unstable Angina Refractory to Standard Treatment [CAPTURE]) (814) has been completed in the setting of non-ST-elevation ACS.
2. Eptifibatide is a cyclical heptapeptide, which binds to the receptor with a short half-life (818). It has been evaluated in a trial of 11,000 patients with non-ST-elevation ACS, 45% of whom had enzymes positive for myocardial necrosis on admission.
3. Tirofiban is a small nonpeptide compound that also has a short half-life. It has been evaluated in 5147 patients in 2 randomized trials of non-ST-elevation ACS (819,820). In the PRISM-PLUS Study (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) (820), 45% of patients also had positive enzymes for myocardial necrosis.

*New section, page 1353, column 2: new text added to end of paragraph 1, before "Interventional Therapy"*

**Low-molecular-weight heparin and direct antithrombins.** Low-molecular-weight heparin (LMWH) is a subfraction of standard heparin with a greater degree of inhibition of factor Xa relative to thrombin when compared with standard UFH. In addition to its convenience—it can be administered subcutaneously with high bioavailability—LMWH has a number of theoretical benefits over UFH. These include the potential to prevent thrombin generation as well as inhibit thrombin, the lack of a need to monitor with coagulation testing, and a lower rate of heparin-associated thrombocytopenia. Four trials have compared the use of LMWH and UFH for non-ST-elevation ACS (507,838-840). In 2 trials, a clear benefit of LMWH was observed (839,840), whereas in another, LMWH was superior to placebo (507). The fourth trial did not show a clear difference in outcomes (838).

Direct-thrombin inhibitors are now available for use in heparin-induced thrombocytopenia and deep venous thrombosis, but they have not been approved for treatment of ACS. Hirudin, a recombinant protein that is an impor-

tant component of leech saliva, has been studied in many thousands of patients; the results show a consistent reduction in the composite of death and nonfatal MI. Hirulog, a synthetic direct thrombin inhibitor, has been studied in only limited populations.

*Text added to "Interventional Therapy," page 1353, column 2, new paragraph added before paragraph beginning "There is considerable variation . . ."*

Recently, the Veterans Affairs Non-Q-Wave Infarction Strategies In Hospital Trial (VANQWISH) (821) has shed important light on the question of intervention in patients with non-Q-wave infarction. The VANQWISH Trial evaluated a somewhat different population than the Thrombolysis in Myocardial Infarction (TIMI-3B) Trial. VANQWISH investigators randomly assigned to an invasive or conservative strategy 920 patients who did not have a major complication within 24 to 72 hours of onset of symptoms. The ECG criteria required the absence of new Q waves; therefore, the trial included patients with and without ST-segment elevation on admission. The aggressive strategy called for routine cardiac catheterization with revascularization of significant lesions, whereas the conservative strategy used intensive medical therapy; angioplasty was used only in patients with recurrent ischemia or hemodynamic compromise. In this trial of management of non-Q-wave MI, there was a 28% rate of cardiac events during follow-up of 12 to 44 months but no early or late clinical benefit with routine invasive management. There was no difference in the primary end point of combined death or nonfatal MI during the average follow-up of 23 months (138 patients assigned to the invasive strategy versus 123 patients assigned to the conservative strategy,  $P = 0.35$ ). There was a significantly higher rate of death among patients assigned to invasive treatment both at hospital discharge (21 versus 6,  $P = 0.007$ ) and at 1 year (58 versus 36,  $P = 0.025$ ). Concern has been raised about the operative mortality rate observed in the trial (7.7% for the composite group and 11.6% for those assigned to the invasive strategy); however, it has been demonstrated that the centers enrolling patients in the trial had operative mortality rates within the expected range for all centers in the United States.

Although the TIMI-3B and VANQWISH trials did not involve identical populations, both studies failed to support the notion that an aggressive approach to revascularization in non-ST-segment elevation ACS reduces the risk of death or nonfatal MI. A contrary view was expressed in the preliminary report of the Fragmin During Instability in Coronary Artery Disease (FRISC) Trial II presented on March 7, 1999, at the 48th Scientific Sessions of the American College of Cardiology, in New Orleans, Louisiana. The FRISC report indicated that, when combined with an early invasive strategy, the LMWH dalteparin may reduce early events in patients with unstable coronary artery disease. In the open acute phase of the trial, 2267 patients with unstable angina or non-Q-wave MI received daltepa-

rin, 120 IU/kg every 12 hours during the first 5 to 7 days. In the subsequent double-blind phase, 2015 of these patients were randomly assigned to receive subcutaneous dalteparin 5000 to 7500 IU/kg twice daily or placebo for 3 months.

Results at 90 days showed no significant difference between the dalteparin and placebo groups in terms of the primary end point (death or MI); however, during the first 45 days, there was a significant reduction in the primary end point among those receiving dalteparin compared with those receiving placebo (3.7% versus 6.5%, respectively;  $P = 0.003$ ). During the prolonged treatment phase, the incidence of bleeding events was 26% with dalteparin and 10% with placebo. In addition to being randomly assigned to receive dalteparin or placebo, patients enrolled in FRISC II were assigned within 48 hours to invasive or noninvasive early management. The invasive strategy consisted of early coronary angiography (within 2 to 7 days), whereas the noninvasive strategy consisted of exercise testing with referral to coronary angiography if the test was positive or further events warranted it. At 6 months the rate of death or MI in the invasive group was 9.5% versus 12% in a noninvasive group ( $P = 0.045$ ). According to subgroup analyses, men particularly benefited from an early invasive strategy, with the rate of death or MI among invasive versus noninvasive groups at 9.1% versus 13.9%;  $P = 0.002$ .

It will be interesting to learn whether other antithrombotic/antiplatelet therapies will produce an environment in which medical therapy alone will be sufficient or whether it will foster improved results with aggressive interventions, which is being addressed in ongoing clinical trials (822).

*New section, page 1354, column 1: new text added before "Hospital Management"*

**Glucose-insulin-potassium infusion.** Metabolic modulation of AMI patients, originally proposed by Sodi-Pallares (823) in 1962, was recently evaluated in a pilot trial by the Estudios Cardiologicos Latinoamerica (ECLA) Collaborative Group (824) in South America. In this recently reported study, 407 patients admitted within 24 hours of onset of symptoms of a suspected MI, regardless of age or ECG findings, were randomly assigned to either a high-dose infusion of glucose-insulin-potassium (GIK) (25% glucose, 50 IU/L soluble insulin, and 80 mmol/L KCl at a rate of  $1.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for 24 hours) or a low-dose infusion (10% glucose, 20 IU/L soluble insulin, and 50 mmol/L KCl at a rate of  $1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for 24 hours) or usual care. A significant reduction in the composite end point of death, nonfatal severe heart failure (greater than Killip class 2), and nonfatal ventricular fibrillation was observed for the overall study population as well as the 252 patients (62%) who also were treated with reperfusion strategies. This latter group also showed a statistically significant reduction in mortality rate (relative risk [RR], 0.34; CI, 0.78 to 10.1,  $2 P = 0.008$ ). A strong relationship was also found between the time from symptom onset and impact of infusion. A significant reduction in mortality rate

was observed in patients treated  $\leq 12$  hours after symptom onset (RR, 0.43; 95% CI, 0.2 to 0.9;  $P = 0.021$ ). Because these results show that a metabolic modulating strategy is feasible in the early hours of an AMI with a GIK infusion in contemporary practice, it is hoped that an appropriately sized clinical trial will get under way soon. The results may have strong implications for incorporating this rather simple and inexpensive therapy for the routine care of AMI patients worldwide.

*New text added to "Triage of Patients With Acute Myocardial Infarction and Other Coronary Syndromes," page 1357, column 2: new paragraph added after line 37, "... and treatment success."*

Two large studies have been published that support these concerns (210,825). A survey of 7560 nurses from across the United States suggests that nurses are caring for increasing numbers of patients and are required to cross-train for more responsibilities; 74% report having less time to teach patients and families, and 69% report less time to provide basic nursing care. Forty-nine percent reported that registered nurses working on a part-time or temporary basis have replaced full-time staff, and 36% reported an increase in nonlicensed assistive personnel. Staffing and perceived quality of care were significantly lower in the Pacific and northeastern regions of the country, where managed care is prevalent (210).

Objective data on quality outcomes were obtained from the American Nurses' Association (825) from a recent study of 502 hospitals in California, Massachusetts, and New York. These data demonstrated that adverse outcomes (ie, pressure ulcers, pneumonia [not community acquired], urinary-tract infections, and postoperative infections) and hospital lengths of stay were associated with RN staffing levels. Adverse events were higher in institutions with lower RN staffing levels. As RN staffing levels decreased, patient length of stay increased, presumably because of adverse events.

A recent report on the adequacy of staffing from the Institute of Medicine (826) concluded that there was sufficient evidence from several studies using different types of quality measures to conclude that there is a positive relationship between nursing-staff levels and the quality of care in nursing homes. The evidence is not sufficient, however, to conclude that such a relationship exists in hospitals. It has been suggested that patient variables (eg, severity of illness) contribute significantly to the variance in outcome and that adverse events may be a more sensitive marker of differences in organizational quality (ie, collaboration, leadership, organizational culture, job satisfaction) than staffing ratios (827,828). Taken together, the research in this area suggests that adverse events are not simply the result of changes in staffing levels but more a function of fundamental changes in institutions as a result of reorganization and restructuring. If so, quality-monitoring activities

in hospitals will be essential as the current trend in managed care penetrates the rest of the country.

*Text added to "Management of Mechanical Defects After AMI," page 1370, column 2: new text replaces first 2 sentences of paragraph beginning "Coronary angiography can..."*

Coronary arteriography can delineate the presence of surgically correctable coronary artery disease, and cardiac catheterization may better delineate the presence of a mechanical defect if other studies are not clear. However, the evidence for concomitant CABG associated with surgical repair of an acute ventricular septal defect (VSD) is inconclusive (829). Although there is a need to minimize invasive angiographic procedures before early surgical correction of the ruptured septum, initial coronary arteriography to assess the coronary anatomy seems warranted in most cases.

*Text added to "Postinfarction Ventricular Septal Defect," page 1371, column 1: new text replaces paragraph*

Increased frequency of acute rupture of the interventricular septum (VSD) as well as earlier presentation may be noted in patients who have undergone thrombolytic therapy (383). Although emergency surgical repair was formerly thought to be necessary only in patients with pulmonary edema or cardiogenic shock, it is now recognized as equally important in hemodynamically stable patients (384,385,830). Because all septal perforations are exposed to sheer forces and necrotic tissue removal processes by macrophages, the rupture site can abruptly expand, resulting in sudden hemodynamic collapse even in patients who appear to be clinically stable with normal left ventricular function (830). For this reason, prompt insertion of an intra-aortic balloon pump and referral for emergency operation are recommended for every patient with acute VSD as soon as the septal rupture is diagnosed. Simultaneous CABG, if feasible, seems warranted in patients with extensive coronary artery disease (386).

*Section renamed and text added, page 1374, column 2: new text added as a second paragraph under new head*

## TICLOPIDINE AND CLOPIDOGREL

In 1 trial, ticlopidine has been shown to be more effective than placebo (no aspirin) in reducing the occurrence of vascular death or MI at 6 months in patients with unstable angina (441). Of note, there was no difference in the number of events over the first 7 to 10 days, a finding consistent with the delayed onset of the antiplatelet effect. Ticlopidine has been approved for clinical use in patients with cerebral ischemia when aspirin has failed, cannot be tolerated, or is contraindicated. However, 2 serious side effects associated with its use have been observed: Reversible neutropenia has been observed when treatment continues for  $>2$  weeks. Ticlopidine can also cause thrombotic thrombocytopenic purpura (TTP). Several cases of TTP have

**Replacement Table 8.** Comparison of Approved Thrombolytic Agents

	Streptokinase	Anistreplase	Alteplase	Reteplase
Dose	1.5 MU in 30–60 min	30 mg in 5 min	100 mg in 90 min	10 U × 2 over 30 min
Bolus administration	No	Yes	No	Yes
Antigenic	Yes	Yes	No	No
Allergic reactions (hypotension most common)	Yes	Yes	No	No
Systemic fibrinogen depletion	Marked	Marked	Mild	Moderate
90-min patency rates (%)	≈50	≈65	≈75	≈75
TIMI grade 3 flow (%)	32	43	54	60
Mortality rate in most recent comparative trials (%)	7.3	10.5	7.2	7.5
Cost per dose (US\$)	\$294	\$2116	\$2196	\$2196

TIMI = Thrombolysis in Myocardial Infarction.

been reported, and in a review of 60 cases, 20% occurred after only 3 to 4 weeks of therapy, but only 3% of patients treated for ≤14 days developed TTP. Furthermore, mortality is high: ≈50% of untreated cases and 25% of treated cases (830a).

Ticlopidine and clopidogrel are ADP-receptor antagonists and quite similar chemically. However, TTP has not been reported with use of clopidogrel, and in the large CAPRIE Trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) (831), the incidence of a significant reduction in neutrophils was only 0.10% in the clopidogrel group and actually slightly higher, at 0.17%, in the aspirin group. In that trial, there was a statistically significant relative risk reduction in vascular death, MI, or stroke of 8.7% in favor of clopidogrel. For these reasons, in many catheterization laboratories, ticlopidine has been replaced with clopidogrel combined with aspirin for the prevention of adverse cardiac events after stent implantation. The effectiveness of this regimen, however, is unknown. Clopidogrel is also preferable to ticlopidine for patients who demonstrate aspirin resistance or for whom aspirin is contraindicated because of hypersensitivity.

*Text added to "Thrombolytic Agents: General Mechanisms of Action and Pharmacological Properties," page 1375, column 2: text added between paragraph ending "...center of plasmin," and paragraph beginning "Aside from this..."*

Aside from this similarity, some comparative features of the Food and Drug Administration-approved thrombolytic agents for intravenous therapy (streptokinase, anistreplase, alteplase, and reteplase) are presented in the revised Table 8. Streptokinase and urokinase are approved for intracoronary use, but this route of administration for AMI is now virtually obsolete. In addition, newer agents have been developed (eg, TNK-tissue plasminogen activator [TNK-tPA] and lanetoplasme). Recent trials with alteplase have used an accelerated regimen given over 90 minutes. The accelerated regimen leads to the highest patency rate without an

increase in ICH and has become the preferred method of administration. The advantage of reteplase is that it can be given by bolus, which is convenient. A recent trial compared the effectiveness and safety of continuous infusion versus double-bolus administration of alteplase (832). The trial was stopped prematurely because of concern about the safety of the double-bolus injection. The rate of hemorrhagic stroke was 1.12% after double-bolus injection of alteplase compared with 0.81% after accelerated infusion of alteplase.

*Text added to "Comparative Thrombolytic Efficacy," page 1376, column 2: new paragraph added before "Considerations in Selecting Thrombolytic Regimens"*

Since the initial publication of these guidelines, the Food and Drug Administration has approved the fibrinolytic agent reteplase for use. Reteplase, a mutant of wild-type tPA, has a longer half-life than its parent molecule and has been compared with alteplase in a large clinical trial (833). An angiographic trial (834) found that 60- and 90-minute TIMI grade 3 flow and coronary patency rates were higher with reteplase than with the accelerated dose of alteplase. When compared with an accelerated infusion of alteplase, reteplase did not provide any additional survival benefit. The mortality rate at 30 days was 7.5% for reteplase and 7.2% for alteplase; and the rates of the combined end point, death or nonfatal MI-disabling stroke, were 7.98% and 7.91%, respectively.

*Text added to "Considerations in Selecting Thrombolytic Regimens," page 1376, column 2: text added as first paragraph*

GUSTO-I (228), GUSTO-III (833), and other recent studies (467,468) suggest that accelerated alteplase and reteplase with intravenous heparin are currently the most effective therapies for achieving early coronary reperfusion, but both are substantially more expensive and carry a slightly greater risk of ICH than streptokinase. Thus, the cost-benefit ratio is greatest in patients presenting early after onset of chest pain or symptoms and in those with a large

area of injury (eg, anterior infarction) and at low risk of ICH. Other promising thrombolytic agents under investigation are TNK-tPA and lanetoplasmin, both of which are mutant forms of wild-type tPA and can be given as a single bolus.

Two equivalence trials comparing these agents with the accelerated infusion of alteplase reported preliminary results in March 1999 at the 48th Scientific Sessions of the American College of Cardiology.

Data from the In TIME-II Study showed the single-bolus thrombolytic lanetoplasmin (nPA) was as effective in reducing the 30-day mortality rate as tPA in patients with AMI. The trial randomly assigned 15,078 patients within 6 hours of symptom onset to receive single-bolus lanetoplasmin (120,000 U/kg) or front-loaded alteplase (up to 100 mg). The 30-day mortality rate (primary end point) in the nPA and tPA groups was 6.7% and 6.6%, respectively. At 24 hours, mortality was slightly lower with nPA than with tPA (2.39% versus 2.49%). The nPA group had a significantly higher incidence of ICH than the tPA group (1.13% versus 0.62%;  $P = 0.003$ ).

The ASSENT-2 trial reported preliminary results from TNK-tPA, the other novel thrombolytic agent delivered by single bolus (790). Within 6 hours of symptom onset, 16,950 patients with AMI were randomly assigned to weight-adjusted TNK-tPA or accelerated tPA. The 30-day mortality rate was 6.17% in the TNK-tPA group and 6.18% in the accelerated tPA group. The incidence of total stroke was similar (1.78% versus 1.66%) as was hemorrhagic stroke (0.93% versus 0.94%), and mild to moderate bleeding was observed less often in the TNK-tPA group than in the tPA group (26% versus 28.1%;  $P < 0.002$ ). Although the efficacy of these agents appears to be equivalent to tPA, it will be important to carefully assess the adverse event rates when these studies are published.

There is considerable ongoing investigation of the effectiveness of thrombolytic therapy alone compared with the combination of either direct-acting antithrombins or the GP IIb/IIIa receptor antagonists as a means to improve effectiveness over the currently available regimen. In 2 studies that evaluated the combination of hirudin (desirudin) with alteplase and streptokinase, there was no improvement in mortality rate, and the therapeutic-to-severe bleeding profile appeared to be very close (TIMI-9 and GUSTO-IIb trials).

Over the past few years, there has been an increase in the number of patients who undergo primary angioplasty for treatment of AMI in hospitals with tertiary cardiac facilities. This has been driven to a large extent by the observed higher patency in TIMI-3 flow rates associated with coronary angioplasty as well as the desire of cardiologists to assess coronary anatomy and ventricular function early in patient management. Still, however, this represents only a small portion of patients with AMI, and thrombolytic therapy remains the major means of reperfusion.

*New text added to "Current Use Rates for Thrombolytic Therapy," page 1377, column 1: new text replaces paragraph 1*

The industry-sponsored NRMI tracks the use of thrombolytic therapy in the United States and has enrolled 330,928 patients treated at 1470 US hospitals during its second phase (NRMI-2) from June 1994 through July 1996. Barron et al (789) recently reported an analysis of this database, attempting to determine what proportion of patients with an MI who are eligible for reperfusion therapy do not receive this proven treatment. Barron used a conservative definition of thrombolytic eligibility (diagnostic changes on ECG or LBBB  $\leq 6$  hours after onset of symptoms and no contraindication to thrombolytic therapy indicated); investigators found that 31% of their cohort were eligible for reperfusion therapy; 25% had nondiagnostic initial ECGs; 41% presented  $>6$  hours from onset of symptoms, and 3% had contraindications to thrombolytic therapy.

Of those who were eligible for thrombolytic therapy, 24% did not receive any form of reperfusion therapy (7.5% of all patients). Multivariate analysis revealed that the independent predictors for eligible patients not being given reperfusion therapy were the presence of LBBB, the disappearance of chest pain at the time of presentation, age  $>75$  years, female gender, and various preexisting cardiovascular conditions. Perhaps most disconcerting was the finding that patients with the highest risk of death from AMI were the least likely to receive reperfusion therapy (eg, patients with a history of congestive heart failure or the presence of LBBB). Both groups had an in-hospital mortality rate of  $\approx 20\%$ , well above the mortality rate of 7.9%, yet the presence of LBBB made it 78% less likely that a patient would receive reperfusion therapy than patients who presented with ST-segment elevation.

*New section, page 1380, column 1: new text added before paragraph beginning "Newer direct antithrombin . . ."*

**Low-molecular-weight heparins.** LMWH preparations are formed by controlled enzymatic or chemical depolymerization-producing saccharide chains of varying length but with a mean molecular weight of  $\approx 5000$  (835). A critical chain length of 18 saccharides is required to form the ternary complex consisting of a heparin fragment, antithrombin, and thrombin. In addition to the critical pentasaccharide sequence discussed above and required for attachment of a heparin fragment to antithrombin, an additional 13 saccharide residues are necessary to allow the heparin fragment to simultaneously attach to the heparin-binding domain of thrombin and create the ternary complex (836). Creation of short-chain or LMWH fragments  $<18$  saccharides in length retain the critical pentasaccharide sequence but are of insufficient length to permit attachment to the heparin-binding domain of thrombin, and therefore thrombin is not inhibited by such short-chain fragments. However, only the critical pentasaccharide sequence is

required for binding to antithrombin and inhibition of factor Xa. Thus, through the creation of a mixture of short- and long-chain heparin fragments, preparations of varying antiXa:antiIIa activity may be developed. Additional features of LMWHs of particular clinical relevance are a decreased sensitivity to platelet factor IV, a more stable, reliable anticoagulant effect, and lower rates of thrombocytopenia and heparin-induced thrombocytopenia syndrome. Thus, LMWHs are clinically attractive because of better bioavailability, ease of administration via the subcutaneous route, and enriched anti-Xa activity (837). Higher anti-Xa activity is important because of the multiplier effect in which 1 molecule of factor Xa leads to production of many molecules of thrombin.

Gurfinkel and colleagues (507) compared placebo treatment, UFH, and the LMWH nadroparin in 219 patients with unstable angina who were also treated with aspirin. Combination therapy with aspirin plus nadroparin significantly reduced the number of patients with an adverse end point event (combined death, MI, and recurrent angina) during the study period, from 59% in the aspirin group and 63% in the aspirin-plus-heparin group to 22% in the aspirin-plus-nadroparin group ( $P < 0.0001$  for comparisons of the nadroparin group with each of the other 2 groups).

The FRISC Trial (506) was designed to determine whether subcutaneous administration of the LMWH dalteparin (Fragmin) would reduce ischemic events during the acute in-hospital period after an episode of unstable angina/non-Q-wave MI. A secondary goal was to determine whether long-term anticoagulation therapy would provide additional benefit compared with anticoagulation restricted only to the acute phase (the first few days after hospitalization) of an acute coronary syndrome. Patients presenting  $\leq 72$  hours after onset of unstable angina/non-Q-wave MI were randomly assigned to receive either dalteparin (120 IU/kg subcutaneously twice daily for 6 days followed by daily subcutaneous injections of 7500 IU for an additional 35 to 45 days;  $n = 746$ ) or placebo ( $n = 760$ ). All patients received aspirin. Compared with the placebo group, dalteparin-treated patients experienced a 63% reduction in death and nonfatal MI at the 6-day evaluation (4.8% in the placebo group compared with 1.8% in the dalteparin group,  $P = 0.001$ ). However, with longer-term follow-up, event rates for the 2 groups began to converge, and a nonsignificant trend toward improved outcome was observed in the dalteparin group (10.7% event rate for the placebo group, compared with 8.0% with dalteparin; RR, 0.75;  $P = 0.07$ ) by 40 days. By 150 days, there was no significant difference between the 2 groups.

The Fragmin in Unstable Coronary Heart Disease (FRIC) Study (838) compared dalteparin with IV heparin in patients with unstable angina/non-Q-wave MI presenting  $\leq 72$  hours after an episode of ischemic chest pain. During the acute phase (the first 6 days after hospitalization), patients received either subcutaneous dalteparin twice daily or UFH infused intravenously during the first 48

hours; during the chronic phase, subcutaneous dalteparin or placebo was continued until day 45. All patients received aspirin throughout the course of the study. The occurrence of the composite outcome of death, MI, or recurrent angina was similar for the UFH and dalteparin groups during the 6-day acute period (7.6% versus 9.3% for the UFH and dalteparin groups, respectively). Similarly, after 45 days, the incidence of death, MI, or recurrent angina was 12.3% for both groups.

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) Study (839) examined the effectiveness of enoxaparin in unstable angina/non-Q-wave MI. In this large, multicenter, double-blind trial, 3171 patients were randomly assigned to receive either twice-daily subcutaneous injections of enoxaparin (1 mg/kg) or continuous intravenous infusion of UFH during the acute period (2 to 8 days) after hospitalization for unstable angina/non-Q-wave MI. The primary end point was a composite of death, MI, or recurrent angina  $\leq 14$  days after hospitalization. The median duration of treatment with the study drug was 2.6 days. The rate of end point events was significantly reduced in the enoxaparin group compared with UFH (16.6% versus 19.8% for the enoxaparin and UFH groups, respectively;  $P = 0.019$ ). The enoxaparin group continued to have fewer events than the UFH group through 30 days, at which time a primary end point event had occurred in 19.8% of the enoxaparin group and 23.3% of the UFH group ( $P = 0.016$ ). Patients treated with enoxaparin were also significantly less likely to require revascularization procedures within 30 days (27.0% versus 32.2%;  $P = 0.001$ ). A cost-effectiveness analysis showed that despite a small increase in drug cost (\$75 per patient), the lower rate of cardiac catheterization and revascularization procedures led to a savings of \$1172 per patient if enoxaparin was used instead of UFH.

Although LMWHs share many pharmacological similarities, they also vary in important respects, and it is important to consider each drug individually rather than as members of a class of interchangeable compounds. The varying effectiveness of these drugs in clinical trials may reflect differing anti-Xa:anti-IIa ratios (835). For example, nadroparin and enoxaparin, both of which have been shown to reduce ischemic events after unstable angina or unstable angina/non-Q-wave MI, have in vitro anti-Xa:anti-IIa ratios between 3 and 4; dalteparin, which appeared to be less effective, has an anti-Xa:anti-IIa ratio of  $\approx 2.2$ . It is not clear to what extent these pharmacological parameters influence the clinical usefulness of the various LMWHs. However, it is also possible that the lack of sustained effect of LMWH in the FRISC and FRIC trials was due to the long patient-enrollment period after the last episode of qualifying chest pain (72 hours in both studies), in contrast to a 24-hour enrollment period used in most other studies.

TIMI-11A (840) was a dose-finding study to assess the safety and tolerability of 2 enoxaparin doses in patients with unstable angina/non-Q-wave MI. The incidence of major

hemorrhage was 6.5% in patients who received 1.25 mg/kg enoxaparin subcutaneously every 12 hours for 2 to 8 days but decreased to 1.9% in patients receiving 1.0 mg/kg every 12 hours.

TIMI-11B enrolled 4020 patients with unstable angina/non-Q-wave MI to compare 2 strategies of antithrombotic therapy: UFH during the acute phase followed by placebo subcutaneous injections during the chronic phase versus uninterrupted therapy with subcutaneous enoxaparin during both the acute and chronic phases (840a). The primary efficacy end point is the occurrence through day 43 of the sum of death/nonfatal MI not present at enrollment or severe recurrent ischemia requiring urgent revascularization. The primary safety end point is the development of major hemorrhage or serious adverse event(s) related to study drug.

Kaplan-Meier curves of the primary end point showed a lower rate of events beginning 8 hours after randomization in the enoxaparin-treated patients. At 48 hours there was a statistically significant 24% relative risk reduction from 7.3% in the UFH group to 5.5% in the enoxaparin group. The superiority of enoxaparin was seen in both patients who were treated with UFH and were outside the target aPTT range and patients who were in the target aPTT range. By 14 days, the rate of death/MI/urgent revascularization was 16.7% in the UFH group and 14.2% in the enoxaparin group, a relative risk reduction of 15% ( $P = 0.03$ ). All individual elements of the composite end point were reduced in the enoxaparin group.

After treatment in the acute phase, eligible patients entered the long-term phase. Kaplan-Meier curves continued through day 43 showed maintenance of the initial benefit in favor of enoxaparin but no additional relative decrease in events during long-term treatment with enoxaparin compared with placebo.

*New section, page 1380, column 1: text added before the paragraph beginning "Newer direct antithrombin . . ."*

## CONCLUSION

Enoxaparin for the acute management of patients with unstable angina/non-Q-wave MI has been shown to be superior to UFH for reducing death and serious cardiac ischemic events. This superiority is achieved without an increase in the rate of either spontaneous or instrumented major hemorrhage. The initial benefit observed with enoxaparin is sustained through day 43; however, no further relative decrease in events was observed in the chronic phase. There was an increase in the rate of major hemorrhage (both spontaneous and instrumented) with long-term enoxaparin treatment.

*New section, page 1380, column 1: new text before paragraph beginning "Newer direct antithrombin . . ."  
(text follows new Conclusion)*

**Low-molecular-weight heparins as an adjunct to thrombolysis.** Another phase II trial in progress, the Hypertension Audit of Risk Factor Therapy (HART-II) Trial, is comparing enoxaparin with UFH as adjunctive antithrombin therapy for patients receiving a front-loaded tPA regimen for ST-segment elevation MI. The primary end point is TIMI-3 flow 90 minutes after initiation of thrombolytic therapy.

*Text added to "Secondary Prevention," page 1396, column 1: new paragraph added before "These results firmly . . ."*

Recently, the results of the large Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study have been reported. More than 9000 patients are randomly assigned to either placebo or 40 mg pravastatin daily. The trial was carried out in a group of patients with a prior history of MI or unstable angina. It was stopped prematurely because of the efficacy of pravastatin in reducing major cardiovascular events, including a 24% decrease in coronary heart disease deaths, a 23% decrease in the total mortality rate, and a 20% decrease in stroke. Benefit has also been seen in patients with symptomatic coronary disease who were treated with fluvastatin. In the Lescol in Severe Atherosclerosis (LiSA) Study, patients with symptomatic coronary heart disease and hypercholesterolemia who were given fluvastatin had 71% fewer cardiac events than those in the placebo group. These results firmly establish the desirability of lowering atherogenic serum lipid levels among patients who have recovered from AMI.

*Text added to "Smoking Cessation," page 1397, column 1: new paragraph added before "Long-Term Use of Aspirin"*

A new drug, bupropion, has been shown to help some smokers quit. Nicotine intake is reinforced by activating the central nervous system to release norepinephrine, dopamine, and other neurotransmitters. Bupropion is a weak inhibitor of the neuronal uptake of neurotransmitters. A study of 615 subjects randomly assigned to take placebo or bupropion achieved good initial quit rates with treatment augmented by brief counseling at baseline, weekly during treatment, and intermittently for up to 1 year (841). Seven weeks of treatment with bupropion was associated with a quit rate of 28.8% (100 mg), 38.6% (150 mg), and 44.2% (300 mg/d); 19.6% of subjects assigned to placebo quit ( $P < 0.001$ ). At 1 year, 12.4% of the placebo group and 19.6% (100 mg), 22.9% (150 mg), and 23.1% (300 mg) of the bupropion group remained abstinent. The drug was well tolerated (37 of 462 [8%] stopped treatment prematurely because of headache, insomnia, or dry mouth), although insufficiently powered to detect an incidence of seizures known to occur with related medications. It reduced the weight gain com-

mon in smokers who quit. Bupropion appears to be another option for patients who need to quit smoking after AMI.

*New section, page 1398, column 1: new text added before "Antioxidants"*

**Quality care alert.** Indeed, the data supporting the beneficial effect of the long-term use of  $\beta$ -blocker therapy after AMI is considered so compelling that the Department of Clinical Quality Improvement of the American Medical Association has circulated a document endorsed by the American College of Cardiology, the American Heart Association, the American College of Physicians, the American Academy of Family Physicians, and numerous other societies. The document provides a synthesis and consensus for the long-term use of  $\beta$ -blockers after AMI. An expert review panel acknowledged that the data for use of  $\beta$ -blockers after non-ST-segment elevated AMI are limited but generally agreed that the totality of evidence demonstrates the following: use of  $\beta$ -blockers after AMI 1) decreases cardiovascular mortality, 2) decreases reinfarctions, and 3) increases the probability of long-term survival by up to 40%.

Although relative contraindications once may have been thought to preclude the use of  $\beta$ -blockers in some patients, new evidence suggests that the benefits of  $\beta$ -blockers in reducing reinfarctions and mortality may actually outweigh its risks, even in patients with 1) asthma; 2) insulin-dependent diabetes mellitus; 3) chronic obstructive pulmonary disease; 4) severe peripheral vascular disease; 5) PR interval  $>0.24$  second; and 6) moderate left ventricular failure. It is also emphasized that the use of  $\beta$ -blockers in such patients requires careful monitoring of the patient to be certain that adverse events do not occur (842-849).

*Text added to "Estrogen Replacement Therapy and Myocardial Infarction," page 1399, column 2: new text replaces paragraphs beginning "In 1993 the American Heart Association . . ." through "Given the overall . . ."*

The first large-scale, randomized, double-blind, placebo-controlled trial that addresses the question of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women was recently published by Hulley et al (791) for the Heart and Estrogen-Progestin Replacement Study (HERS) Research Group. Contrary to conventional wisdom and several observational studies (761-764), this trial of 3763 postmenopausal women with established coronary disease and an average age of 66.7 years found no reduction in overall risk for nonfatal MI or coronary death, nor any other cardiovascular outcome, during an average of 4.1 years of follow-up while taking either 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate in 1 tablet daily ( $n = 1380$ ) or placebo ( $n = 1383$ ).

This lack of an overall effect occurred despite a net 11% lower low-density lipoprotein (LDL) cholesterol level and a 10% higher high-density lipoprotein (HDL) cholesterol in the group given hormone therapy compared with the placebo group ( $P < 0.001$ ). There was a statistically significant time trend, however, with more primary coronary events in the hormone therapy group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 versus 12; RR, 2.89; 95% CI, 1.50 to 5.58) and gallbladder disease (84 versus 62; RR, 1.38; 95% CI, 1.00 to 1.92). On the basis of the finding of no overall cardiovascular benefit and a pattern of early increase in risk of coronary events, it was concluded that starting estrogen plus progestin should not be recommended for the purpose of secondary prevention of coronary disease in postmenopausal women after an AMI. However, given the favorable pattern of coronary events after several years of therapy, it was considered appropriate for women already receiving treatment to continue.

This study did not evaluate the cardiovascular effect of treatment with unopposed estrogen, which is commonly used in women who have had a hysterectomy, or other estrogen plus progestin formulations. This study also did not investigate women without coronary disease. Other randomized trials of postmenopausal hormone therapy are likely to answer some of the questions raised by HERS. The Women's Health Initiative Hormone Replacement Trial (HRT) includes a group of women who have had hysterectomies and received unopposed estrogen as well as women with intact uteruses who receive the same estrogen plus progestin used in HERS. Participants are not required to have coronary heart disease and are generally younger than those in the HERS cohort. The HRT has completed its enrollment of 27,348 women and plans to report the results of the trial in 2005 after 9 years of treatment.

The dose of estrogen for postmenopausal women who have had a hysterectomy is usually 0.625 mg oral conjugated estrogen or its equivalent once a day. In postmenopausal women with a uterus, 2 dosing schedules are commonly used: 0.625 mg conjugated estrogen or its equivalent once a day plus 10 mg progestin (medroxyprogesterone) orally per day for 10 to 14 days each month or 2.5 mg progestin orally every day. Screening procedures for women without a uterus who are taking estrogen are no different than for the nontreated population. Women who take cyclic progestins and develop bleeding other than at time of withdrawal or women who take continuous progestin and develop heavy, prolonged, frequent, or intermittent bleeding lasting  $>10$  months after the start of progestin should be evaluated (765).

There is overall uncertainty about the true benefit of estrogen replacement therapy after MI in women. Therefore, after careful counseling about the risk/benefit issues of hormone replacement therapy, patient preference should be the dominant factor in making any decision.

**ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction  
1999 Update: Revisions and Additions to Recommendations**

The following is a listing of the specific recommendations that have been revised:

JACC page no.	CIRC page no.	Original Recommendation (1996)	Revised Recommendation (1999)
1344	2344	<p><b>Aspirin</b> <i>Class IIb</i></p> <p>1. Other antiplatelet agents such as dipyridamole or ticlopidine may be substituted if true aspirin allergy is present.</p>	<p><b>Aspirin</b> <i>Class IIb</i></p> <p>1. Other antiplatelet agents such as dipyridamole, ticlopidine, or clopidogrel may be substituted if true aspirin allergy is present or if the patient is unresponsive to aspirin.</p>
1348-49	2345	<p><b>Primary PTCA</b> <i>Class I</i></p> <p>1. As an alternative to thrombolytic therapy only if performed in a <i>timely fashion by individuals skilled in the procedure† and supported by experienced personnel in high-volume centers.‡</i></p> <p><i>Class IIa</i></p> <p>1. As a reperfusion strategy in patients who are candidates for reperfusion but who have a <i>risk of bleeding contraindication to thrombolytic therapy</i> (Table 3).</p> <p>2. Patients in cardiogenic shock.</p> <p><i>Class IIb</i></p> <p>1. As a reperfusion strategy in patients who fail to qualify for thrombolytic therapy for reasons other than a risk of bleeding contraindication.</p> <p><i>Class III</i></p> <p>New.</p>	<p><b>Primary PTCA</b> <i>Class I</i></p> <p>1. As an alternative to thrombolytic therapy in patients with AMI and ST-segment elevation or new or presumed new LBBB who can undergo angioplasty of the infarct-related artery within 12 hours of onset of symptoms or beyond 12 hours if ischemic symptoms persist, if performed in a <i>timely fashion*</i> by persons skilled in the procedure† and supported by experienced personnel in an appropriate laboratory environment.‡</p> <p>*Performance standard: balloon inflation within 90 (<math>\pm 30</math>) minutes of admission.</p> <p>†Individuals who perform &gt;75 PTCA procedures per year.</p> <p>‡Centers that perform &gt;200 PTCA procedures per year and have cardiac surgical capability (110).</p> <p>2. In patients who are within 36 hours of an acute ST-elevation/Q-wave or new LBBB MI who develop cardiogenic shock are &lt;75 years old, and revascularization can be performed within 18 hours of onset of shock.</p> <p><i>Class IIa</i></p> <p>1. As a reperfusion strategy in candidates for reperfusion who have a contraindication to thrombolytic therapy (Table 3).</p> <p><i>Class IIb</i></p> <p>1. In patients with AMI who do not present with ST elevation but who have reduced (less than TIMI grade 2) flow of the infarct-related artery and when angioplasty can be performed within 12 hours of onset of symptoms.</p> <p><i>Class III</i></p> <p>This category applies to patients with AMI who</p> <ol style="list-style-type: none"> <li>Undergo elective angioplasty of a non-infarct-related artery at the time of AMI</li> <li>Are beyond 12 hours after onset of symptoms and have no evidence of myocardial ischemia</li> <li>Have received fibrinolytic therapy and have no symptoms of myocardial ischemia</li> <li>Are eligible for thrombolysis and are undergoing primary angioplasty performed by a low volume operator in a laboratory without surgical capability</li> </ol>

JACC page no.	CIRC page no.	Original Recommendation (1996)	Revised Recommendation (1999)
1352	2345	<p><b>Early Coronary Angiography and/or Interventional Therapy</b></p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Patients with recurrent (stuttering) episodes of spontaneous or induced ischemia or evidence of shock, pulmonary congestion, or LV dysfunction.</li> </ol> <p><i>Class IIa</i></p> <ol style="list-style-type: none"> <li>Patients with persistent ischemic-type discomfort despite medical therapy and an abnormal ECG or <math>\geq 2</math> risk factors for coronary artery disease.</li> <li>Patients with chest discomfort, hemodynamic instability, and an abnormal ECG.</li> </ol> <p><i>Class IIb</i></p> <ol style="list-style-type: none"> <li>Patients with chest discomfort and an unchanged ECG.</li> <li>Patients with ischemic-type chest discomfort and a normal ECG and <math>&gt;2</math> risk factors for coronary artery disease.</li> </ol>	<p><b>Early Coronary Angiography and/or Interventional Therapy</b></p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Patients with persistent or recurrent (stuttering) episodes of symptomatic ischemia, spontaneous or induced, with or without associated ECG changes.</li> <li>Presence of shock, severe pulmonary congestion, or continuing hypotension.</li> </ol> <p><i>Class IIa</i></p> <p>None.</p> <p><i>Class IIb</i></p> <p>None.</p>
New	New		<b>Glycoprotein IIb/IIIa Inhibitors</b>
1368-69	2348	<p><b>Emergency or Urgent Cardiac Repair of Mechanical Defects</b></p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Postinfarction VSD or free wall rupture and pulmonary edema or cardiogenic shock (emergency or urgent).</li> </ol>	<p><b>Emergency or Urgent Cardiac Repair of Mechanical Defects</b></p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Postinfarction VSD or free wall rupture.</li> </ol>
1377-78	2348	<p><b>Heparin</b></p> <p><i>Class IIa</i></p> <ol style="list-style-type: none"> <li>Intravenously in patients undergoing reperfusion therapy with alteplase. <i>Comment: The recommended regimen is 70 U/kg as a bolus at initiation of alteplase infusion, then an initial maintenance dose of <math>\approx 15 \mu\text{g}/\text{kg}</math> per hour, adjusted to maintain aPTT at 1.5 to 2.0 times control (50 to 75 seconds) for 48 hours (Table 9). Continuation of heparin infusion beyond 48 hours should be restricted to patients at high risk for systemic or venous thromboembolism.</i></li> <li>(new text)</li> </ol>	<p><b>Unfractionated Heparin</b></p> <p><i>Class IIa</i></p> <ol style="list-style-type: none"> <li>Intravenously in patients undergoing reperfusion therapy with alteplase. <i>Comment: The recommended regimen is 60 U/kg as a bolus at initiation of alteplase infusion, then an initial maintenance dose of <math>\approx 12 \text{ U}/\text{kg}</math> per hour (with a maximum of 4000 U bolus and 1000 U/h infusion for patients weighing <math>&gt;70 \text{ kg}</math>), adjusted to maintain aPTT at 1.5 to 2.0 times control (50 to 70 seconds) for 48 hours (Table 9). Continuation of heparin infusion beyond 48 hours should be considered in patients at high risk for systemic or venous thromboembolism.</i></li> </ol>

JACC page no.	CIRC page no.	Original Recommendation (1996)	Revised Recommendation (1999)
1381-82	2348	<p><b><math>\beta</math>-Adrenoceptor Blocking Agents</b></p> <p><b>Early Therapy</b> (see also "Predischarge Preparation")</p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Patients without a contraindication to <math>\beta</math>-adrenoceptor blocker therapy who can be treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy.</li> <li>(new text)</li> </ol> <p><i>Class IIb</i></p> <ol style="list-style-type: none"> <li>Non-Q-wave MI.</li> </ol> <p><i>Class III</i></p> <ol style="list-style-type: none"> <li>Patients with moderate or severe LV failure or other contraindications to <math>\beta</math>-adrenoceptor blocker therapy.</li> </ol>	<p><b><math>\beta</math>-Adrenoceptor Blocking Agents</b></p> <p><b>Early Therapy</b></p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Patients without a contraindication to <math>\beta</math>-adrenoceptor blocker therapy who can be treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy or performance of primary angioplasty.</li> <li>Non-ST-elevation MI.</li> </ol> <p><i>Class IIb</i></p> <ol style="list-style-type: none"> <li>Patients with moderate LV failure (the presence of bibasilar rales without evidence of low cardiac output) or other relative contraindications to <math>\beta</math>-adrenoceptor blocker therapy, provided patients can be monitored closely.</li> </ol> <p><i>Class III</i></p> <ol style="list-style-type: none"> <li>Patients with severe LV failure.</li> </ol>
1382	2348	<b>Angiotensin-Converting Enzyme Inhibitors</b>	<p><b>Angiotensin-Converting Enzyme Inhibitors</b></p> <p><i>Class I</i></p> <ol style="list-style-type: none"> <li>Patients within the first 24 hours of a suspected AMI with ST-segment elevation in <math>\geq 2</math> anterior precordial leads or with clinical heart failure in the absence of significant hypotension or known contraindications to use of ACE inhibitors.</li> </ol>
1395	2349-50	<p><b>Management of Lipids</b></p> <p><i>Class IIb</i></p> <ol style="list-style-type: none"> <li>Drug therapy using either niacin or gemfibrozil may be added to diet regardless of LDL and HDL levels when triglyceride levels are <math>&gt; 400</math> mg/dL.</li> </ol>	<p><b>Management of Lipids</b></p> <p><i>Class IIb</i></p> <ol style="list-style-type: none"> <li>Drug therapy with either niacin or gemfibrozil may be added to diet regardless of LDL and HDL levels when triglyceride levels are <math>&gt; 200</math> mg/dL.</li> </ol>

JACC page no.	CIRC page no.	Original Recommendation (1996)	Revised Recommendation (1999)
1397	2350	<b>β-Adrenoceptor Blockers</b> <b>Long-Term Therapy in Survivors of Myocardial Infarction</b> <i>Class IIa</i> 2. (new text) <i>(Class IIb New.)</i> <i>Class III</i> 1. Patients with a contraindication to β-adrenoceptor blocker therapy.	<b>β-Blocker</b> <b>Long-Term Therapy in Survivors of Myocardial Infarction</b> <i>Class IIa</i> 2. Survivors of non-ST-elevation MI. <i>Class IIb</i> 1. Patients with moderate or severe LV failure or other relative contraindication to β-adrenoceptor blocker therapy, provided patients can be monitored closely. <i>Class III</i> None.
1399	2350	<b>Estrogen Replacement Therapy and Myocardial Infarction</b> <i>Class IIa</i> 1. All postmenopausal patients who have an MI should be carefully counseled about the potential beneficial effects of ERT and offered the option of ERT if they desire it.	<b>Estrogen Replacement Therapy and Myocardial Infarction</b> <i>Class IIa</i> 1. HRT with estrogen plus progestin for secondary prevention of coronary events should not be given <i>de novo</i> to postmenopausal women after AMI. 2. Postmenopausal women who are already taking HRT with estrogen plus progestin at the time of AMI can continue this therapy.

ACE = angiotensin-converting enzyme, AF = atrial fibrillation, AMI = acute myocardial infarction, BP = blood pressure, Circ = Circulation, ECG = electrocardiogram, ERT = estrogen replacement therapy, HDL = high-density lipoprotein, HRT = hormone replacement therapy, JACC = Journal of American College of Cardiology, LBBB = left bundle-branch block, LDL = low-density lipoprotein, LMWH = low-molecular-weight heparin, LV = left ventricular, PTCA = percutaneous transluminal coronary angioplasty, TIMI = Thrombolysis in Myocardial Infarction, UFH = unfractionated heparin, VSD = ventricular septal defect.

## REPLACEMENT REFERENCES

124. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol* 1998;31:1240-5.
127. Suryapranata H, van't Hof AW, Hoornste JC, de Boer MJ, Zijlstra F. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. *Circulation* 1998;97:2502-5.
210. Shindul-Rothschild J, Berry D, Long-Middleton E. Where have all the nurses gone? Final results of our patient care survey. *Am J Nurs* 1996;96:25-39.
327. Madsen JK, Grande P, Saunamaki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI): DANish trial in Acute Myocardial Infarction. *Circulation* 1997;96:748-55.
497. Zabel KM, Granger CB, Becker RC, et al. Use of bedside activated partial thromboplastin time monitor to adjust heparin dosing after thrombolysis for acute myocardial infarction: results of GUSTO-1. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *Am Heart J* 1998;136:868-76.
504. Hirsh J, Warkentin TE, Raschke R, et al. Heparin and low-molecular heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1998;114 Suppl:489S-510S.
790. Cannon CP, Gibson CM, McCabe CH, et al. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Thrombolysis in Myocardial Infarction (TIMI) 10B Investigators. Circulation* 1998;98:2805-14.
791. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. JAMA* 1998;280:605-13.
792. Tsung SH. Several conditions causing elevation of serum CK-MB and CK-BB. *Am J Clin Pathol* 1981;75:711-5.
793. Tsung JS, Tsung SS. Creatine kinase isoenzymes in extracts of various human skeletal muscles. *Clin Chem* 1986;32:1568-70.
794. Adams JE III, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation* 1993;88:101-6.
795. Mair J, Morandell D, Genser N, et al. Equivalent early sensitivities of myoglobin, creatine kinase MB mass, creatine kinase isoform ratios, and cardiac troponins I and T for acute myocardial infarction. *Clin Chem* 1995;41:1266-72.
796. Antman EM, Grudzien C, Mitchell RN, Sacks DB. Detection of unsuspected myocardial necrosis by rapid bedside assay for cardiac troponin T. *Am Heart J* 1997;133:596-8.
797. Ravkilde J, Horder M, Gerhardt W, et al. Diagnostic performance and prognostic value of serum troponin T in suspected acute myocardial infarction. *Scand J Clin Lab Invest* 1993;53:677-85.
798. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-9.
799. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia: GUSTO IIa investigators. *N Engl J Med* 1996;335:1333-41.
800. Hamm CW, Heeschen D, Goldmann BU, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia [abstr]. *J Am Coll Cardiol* 1998;31:185A.
801. Zimmerman J, Fromm R, Meyer D, et al. Diagnostic marker

## NEW REFERENCES

788. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1998;32:1312-9.
789. Barron HV, Bowbly LJ, Breen T, et al. Use of reperfusion therapy for acute myocardial infarction in the United States: data from the

- cooperative study for the diagnosis of myocardial infarction. *Circulation* 1999;99:1671-7.
802. Ohman EM, Armstrong PW, Weaver WD, et al. Prognostic value of whole-blood qualitative troponin T testing in patients with acute myocardial infarction in the GUSTO-III trial [abstr]. *Circulation* 1998;96:I-216.
803. Tanasijevic M, Cannon CP, Wybenga DR, et al. Myoglobin, creatinine kinase MB, and cardiac troponin-I to assess reperfusion after thrombolysis for acute myocardial infarction: results from TIMI 10A. *Am Heart J* 1997;134:622-30.
804. Antman EM, Sacks DB, Rifai N, et al. Time to positivity of a rapid bedside assay for cardiac-specific troponin T predicts prognosis in acute coronary syndromes: a Thrombolysis in Myocardial Infarction (TIMI) 11A substudy. *J Am Coll Cardiol* 1998;31:326-30.
805. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction: the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy investigators [published erratum appears in *N Engl J Med* 1997;337:287]. *N Engl J Med* 1997;336:1621-8.
- 805a. Hochman JS, Sleeper LA, Webb JG, et al, for the SHOCK Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *New Engl J Med* 1999. In Press.
806. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review [published erratum appears in *JAMA* 1998;279:1876]. *JAMA* 1997;278:2093-8.
807. Yusuf S. Primary angioplasty compared with thrombolytic therapy for acute myocardial infarction. *JAMA* 1997;278:210-1.
808. Grines CL, Morice MD, Mattos L, et al. A prospective multicenter trial using the JJIS heparin-coated stent for reperfusion of acute myocardial infarction [abstr]. *J Am Coll Cardiol* 1998;29:289A.
809. Stone GW. Primary stenting in acute myocardial infarction: the promise and the proof. *Circulation* 1998;97:2482-5.
810. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes: the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb. *N Engl J Med* 1996;335:775-82.
811. Coller BS, Folts JD, Smith SR, Scudder LE, Jordan R. Abolition of in vivo platelet thrombus formation in primates with monoclonal antibodies to the platelet GPIIb/IIIa receptor: correlation with bleeding time, platelet aggregation, and blockade of GPIIb/IIIa receptors. *Circulation* 1989;80:1766-74.
812. Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;332:1553-9.
813. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998;98:2829-35.
814. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study [published erratum appears in *Lancet* 1997;350:744]. *Lancet* 1997;349:1429-35.
815. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty: the EPIC investigation. *N Engl J Med* 1994;330:956-61.
816. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization: the EPILOG investigators. *N Engl J Med* 1997;336:1689-96.
817. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction: ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) investigators. *Circulation* 1998;98:734-41.
818. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes: the PURSUIT Trial investigators. Platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy. *N Engl J Med* 1998;339:436-43.
819. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study investigators. *N Engl J Med* 1998;338:1498-505.
820. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study investigators [published erratum appears in *N Engl J Med* 1998;339:415]. *N Engl J Med* 1998;338:1488-97.
821. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy: Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial investigators. *N Engl J Med* 1998;338:1785-92.
822. Cannon CP, Weintraub WS, Demopoulos LA, et al. Invasive versus conservative strategies in unstable angina and non-Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 Trial: Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy: Thrombolysis in Myocardial Infarction. *Am J Cardiol* 1998;82:731-6.
823. Sodi-Pallares D, Testelli MR, Fischleider BL. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. *Am J Cardiol* 1962;9:166-81.
824. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction: the ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. *Circulation* 1998;98:2227-34.
825. American Nurses' Association. Implementing Nursing's Report Card: A Study of RN Staffing, Length of Stay and Patient Outcomes. Washington, DC: American Nurses Publishing; 1997:1-32.
826. Institute of Medicine (US) Committee on the Adequacy of Nurse Staffing in Hospitals and Nursing Homes. Wunderlich GS, et al, editors. *Nursing Staff in Hospitals and Nursing Homes: Is It Adequate?* Washington, DC: National Academy Press; 1996:1-18.
827. Mitchell PH, Shortell SM. Adverse outcomes and variations in organization of care delivery. *Med Care* 1997;35:NS19-32.
828. Aiken LH, Sochalski J, Lake ET. Studying outcomes of organizational change in health services. *Med Care* 1997;35:NS6-18.
829. Topaz O, DiSciascio G, Vetrovec GW. Acute ventricular septal rupture: perspectives on the current role of ventriculography and coronary arteriography and their implication for surgical repair. *Am Heart J* 1990;120:412-7.
830. Topaz O, Taylor AL. Interventricular septal rupture complicating acute myocardial infarction: from pathophysiologic features to the role of invasive and noninvasive diagnostic modalities in current management. *Am J Med* 1992;93:683-8.
- 830a. Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine. A review of 60 cases. *Ann Intern Med* 1998;128:541-4.
831. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE): CAPRIE Steering Committee. *Lancet* 1996;348:1329-39.
832. A comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction: the Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) investigators. *N Engl J Med* 1997;337:1124-30.
833. A comparison of reteplase with alteplase for acute myocardial infarction: the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) investigators. *N Engl J Med* 1997;337:1118-23.
834. Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction: the RAPID II investigators. *Circulation* 1996;94:891-8.
835. Weitz JI. Low-molecular-weight heparins [published erratum appears in *N Engl J Med* 1997;337:1567]. *N Engl J Med* 1997;337:688-98.
836. Danielsson A, Raub E, Lindahl U, Bjork I. Role of ternary complexes, in which heparin binds both antithrombin and proteinase, in the acceleration of the reactions between antithrombin and thrombin or factor Xa. *J Biol Chem* 1986;261:15467-73.
837. Cannon CP, Antman EM, Crawford MH. Heparin and low-molecular-weight heparin in acute coronary syndromes and angioplasty. In: Crawford MH, editor. *Cardiology Clinics: Annual of Drug Therapy*. Philadelphia: WB Saunders; 1997:105-19.
838. Klein W. Low molecular weight heparin in the initial and prolonged

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839. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;337:447-52.
840. The Thrombolysis in Myocardial Infarction (TIMI) 11A Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. *J Am Coll Cardiol* 1997;29:1474-82.
- 840a. Antman EM, McCabe CH, Gurfinkel EP, et al, for the TIMI 11B Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the thrombolysis in myocardial infarctions (TIMI) 11B trial. *Circulation* 1999. In Press.
841. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195-202.
842. Soumerai SB, McLaughlin TJ, Spiegelman D, et al. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. *JAMA* 1997;277:115-21.
843. Marciniak TA, Ellerbeck EF, Radford MJ, et al. Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *JAMA* 1998; 279:1351-7.
844. Krumholz HM, Radford MJ, Wang Y, et al. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA* 1998;280:623-9.
845. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;339:489-97.
846. Gheorghiade M, Schultz L, Tilley B, Kao W, Goldstein S. Effects of propranolol in non-Q-wave acute myocardial infarction in the beta blocker heart attack trial. *Am J Cardiol* 1990;66:129-33.
847. Guidelines for risk stratification after myocardial infarction. American College of Physicians. *Ann Intern Med* 1997;126:556-60.
848. Peterson ED, Shaw LJ, Califf RM. Risk stratification after myocardial infarction. *Ann Intern Med* 1997;126:561-82.
849. Cardiovascular Disease: Update on Management of Heart Failure, Acute Myocardial Infarction, and Cardiac Arrhythmias. *Am Fam Physician*. Monograph 1. Kansas City, Mo: American Academy of Family Physicians; 1998:1.

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# ACC/AHA Practice Guidelines

## ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction—Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction)

*Developed in Collaboration With the Canadian Cardiovascular Society*

### WRITING COMMITTEE MEMBERS

Elliott M. Antman, MD, FACC, FAHA, Chair; Daniel T. Anbe, MD, FACC, FAHA;  
Paul Wayne Armstrong, MD, FACC, FAHA; Eric R. Bates, MD, FACC, FAHA;  
Lee A. Green, MD, MPH; Mary Hand, MSPH, RN, FAHA; Judith S. Hochman, MD, FACC, FAHA;  
Harlan M. Krumholz, MD, FACC, FAHA; Frederick G. Kushner, MD, FACC, FAHA;  
Gervasio A. Lamas, MD, FACC; Charles J. Mullany, MB, MS, FACC;  
Joseph P. Ornato, MD, FACC, FAHA; David L. Pearle, MD, FACC, FAHA;  
Michael A. Sloan, MD, FACC; Sidney C. Smith, Jr, MD, FACC, FAHA

### TASK FORCE MEMBERS

Elliott M. Antman, MD, FACC, FAHA, Chair; Sidney C. Smith, Jr, MD, FACC, FAHA, Vice-chair;  
Joseph S. Alpert, MD, FACC, FAHA\*; Jeffrey L. Anderson, MD, FACC, FAHA;  
David P. Faxon, MD, FACC, FAHA; Valentin Fuster, MD, PhD, FACC, FAHA;  
Raymond J. Gibbons, MD, FACC, FAHA\*†;  
Gabriel Gregoratos, MD, FACC, FAHA\*; Jonathan L. Halperin, MD, FACC, FAHA;  
Loren F. Hiratzka, MD, FACC, FAHA; Sharon Ann Hunt, MD, FACC, FAHA;  
Alice K. Jacobs, MD, FACC, FAHA; Joseph P. Ornato, MD, FACC, FAHA

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\*Former Task Force member.

†Immediate Past Chair.

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• General Concepts.....	●
• Selection of Reperfusion Strategy .....	●
• Pharmacological Reperfusion.....	●
• Percutaneous Coronary Intervention.....	●
• Acute Surgical Reperfusion .....	●
• Patients With STEMI Not Receiving Reperfusion .....	●
• Assessment of Reperfusion .....	●
• Ancillary Therapy .....	●
• Other Pharmacological Measures .....	●
VII. Hospital Management.....	●
A. Location.....	●
1. Coronary Care Unit .....	●
2. Stepdown Unit .....	●
B. Early, General Measures .....	●
1. Level of Activity .....	●
2. Diet.....	●
3. Patient Education in the Hospital Setting.....	●
4. Analgesia/Anxiolytics.....	●
C. Risk Stratification During Early Hospital Course.....	●
D. Medication Assessment.....	●
1. Beta Blockers.....	●
2. Nitroglycerin .....	●
3. Inhibition of the Renin-Angiotensin-Aldosterone System .....	●
4. Antiplatelets .....	●
5. Antithrombotics .....	●
6. Oxygen.....	●
E. Estimation of Infarct Size .....	●
1. Electrocardiographic Techniques .....	●
2. Cardiac Biomarker Methods .....	●
3. Radionuclide Imaging .....	●
4. Echocardiography .....	●
5. Magnetic Resonance Imaging .....	●
F. Hemodynamic Disturbances .....	●
1. Hemodynamic Assessment .....	●
2. Hypotension .....	●
3. Low-Output State .....	●
4. Pulmonary Congestion .....	●
5. Cardiogenic Shock .....	●
6. Right Ventricular Infarction .....	●
7. Mechanical Causes of Heart Failure/Low-Output Syndrome .....	●
a. Diagnosis .....	●
b. Mitral Valve Regurgitation .....	●
c. Ventricular Septal Rupture After STEMI .....	●
d. Left Ventricular Free-Wall Rupture .....	●
e. Left Ventricular Aneurysm .....	●
f. Mechanical Support of the Failing Heart .....	●
• Intra-Aortic Balloon Counterpulsation .....	●
G. Arrhythmias After STEMI .....	●
1. Ventricular Arrhythmias .....	●
a. Ventricular Fibrillation .....	●
b. Ventricular Tachycardia .....	●
c. Ventricular Premature Beats .....	●
d. Accelerated Idioventricular Rhythms and Accelerated Junctional Rhythms .....	●
e. ICD Implantation in Patients After STEMI .....	●
2. Supraventricular Arrhythmias/Atrial Fibrillation .....	●
3. Bradyarrhythmias .....	●
a. Acute Treatment of Conduction Disturbances and Bradyarrhythmias .....	●
• Ventricular Asystole .....	●
b. Use of Permanent Pacemakers .....	●
• Permanent Pacing for Bradycardia or Conduction Blocks Associated With STEMI .....	●
• Sinus Node Dysfunction After STEMI .....	●
• Pacing Mode Selection in Patients With STEMI .....	●
H. Recurrent Chest Pain After STEMI .....	●
1. Pericarditis .....	●
2. Recurrent Ischemia/Infarction .....	●
I. Other Complications .....	●

1. Ischemic Stroke.....	●
2. DVT and Pulmonary Embolism.....	●
J. Coronary Artery Bypass Graft Surgery After STEMI.....	●
1. Timing of Surgery .....	●
2. Arterial Grafting.....	●
3. CABG for Recurrent Ischemia After STEMI.....	●
4. Elective CABG Surgery After STEMI in Patients With Angina.....	●
5. CABG Surgery After STEMI and Antiplatelet Agents.....	●
K. Convalescence, Discharge, and Post-Myocardial Infarction Care.....	●
1. Risk Stratification at Hospital Discharge.....	●
a. Role of Exercise Testing .....	●
b. Role of Echocardiography .....	●
c. Exercise Myocardial Perfusion Imaging.....	●
d. Left Ventricular Function.....	●
e. Invasive Evaluation.....	●
f. Assessment of Ventricular Arrhythmias .....	●
L. Secondary Prevention.....	●
1. Patient Education Before Discharge .....	●
2. Lipid Management.....	●
3. Weight Management.....	●
4. Smoking Cessation.....	●
5. Antiplatelet Therapy .....	●
6. Inhibition of Renin-Angiotensin-Aldosterone-System .....	●
7. Beta-Blockers.....	●
8. Blood Pressure Control.....	●
9. Diabetes Management.....	●
10. Hormone Therapy .....	●
11. Warfarin Therapy.....	●
12. Physical Activity.....	●
13. Antioxidants .....	●
VIII. Long-Term Management .....	●
A. Psychosocial Impact of STEMI.....	●
B. Cardiac Rehabilitation.....	●
C. Follow-Up Visit With Medical Provider.....	●
References .....	●

## I. Introduction

Although considerable improvement has occurred in the process of care for patients with ST-elevation myocardial infarction (STEMI), room for improvement exists.<sup>1-3</sup> The purpose of the present guideline is to focus on the numerous advances in the diagnosis and management of patients with STEMI since 1999. This is reflected in the changed name of the guideline: "ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction." The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention in patients with STEMI summarize both clinical evidence and expert opinion (Table 1). To provide clinicians with a set of recommendations that can easily be translated into the practice of caring for patients with STEMI, this guideline is organized around the chronology of the interface between the

patient and the clinician. The full guideline is available at <http://www.acc.org/clinical/guidelines/stemi/index.htm>.

## II. Pathology

### A. Epidemiology

STEMI continues to be a significant public health problem in industrialized countries and is becoming an increasingly significant problem in developing countries.<sup>4</sup> Although the exact incidence is difficult to ascertain, using first-listed and secondary hospital discharge data, there were 1 680 000 unique discharges for ACS in 2001.<sup>5</sup> Applying the conservative estimate of 30% of the ACS patients who have STEMI from the National Registry of Myocardial Infarction-4 [NRMI-4],<sup>5a</sup> we estimate 500 000 STEMI events per year in the U.S. This writing committee strongly endorses several public health campaigns that are likely to contribute to a reduction in the incidence of and fatality from STEMI in the future and additional research of new strategies for the management of STEMI patients in the community.<sup>6-13</sup>

## III. Management Before STEMI

### A. Identification of Patients at Risk of STEMI

#### *Class I*

1. Primary care providers should evaluate the presence and status of control of major risk factors for coronary heart disease (CHD) for all patients at regular intervals (approximately every 3 to 5 years). (*Level of Evidence: C*)
2. Ten-year risk (National Cholesterol Education Program [NCEP] global risk) of developing symptomatic CHD should be calculated for all patients who have 2 or more major risk factors to assess the need for primary prevention strategies.<sup>14</sup> (*Level of Evidence: B*)
3. Patients with established CHD should be identified for secondary prevention, and patients with a CHD risk equivalent (eg, diabetes mellitus, chronic kidney disease, or 10-year risk greater than 20% as calculated by Framingham equations) should receive equally intensive risk factor intervention as those with clinically apparent CHD. (*Level of Evidence: A*)

### B. Patient Education for Early Recognition and Response to STEMI

#### *Class I*

1. Patients with symptoms of STEMI (chest discomfort with or without radiation to the arms[s], back, neck, jaw, or epigastrium; shortness of breath; weakness; diaphoresis; nausea; lightheadedness) should be transported to the hospital by ambulance rather than by friends or relatives. (*Level of Evidence: B*)
2. Healthcare providers should actively address the following issues regarding STEMI with patients and their families:
  - a. The patient's heart attack risk (*Level of Evidence: C*)
  - b. How to recognize symptoms of STEMI (*Level of Evidence: C*)
  - c. The advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 minutes, despite feelings of uncertainty about the symptoms and

**TABLE 1.** Applying Classification of Recommendations and Level of Evidence

	"Size of Treatment Effect"			
	Class I	Class IIa	Class IIb	Class III
<b>"Estimate of Certainty (Precision) of Treatment of Effect"</b>  Level A Multiple (3–5) population risk strata evaluated* General consistency of direction and magnitude of effect	<b>Benefit &gt;&gt; Risk</b> <b>Procedure/Treatment SHOULD be performed/administered</b> <ul style="list-style-type: none"> <li>• Recommendation that procedure or treatment is useful/effective</li> <li>• Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<b>Benefit &gt;&gt; Risk</b> <b>Additional studies with focused objectives needed</b> <b>IT IS REASONABLE to perform procedure/administer treatment</b> <ul style="list-style-type: none"> <li>• Recommendation in favor of treatment or procedure being useful/effective</li> <li>• Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<b>Benefit = Risk</b> <b>Additional studies with broad objectives needed; additional registry data would be helpful</b> <b>Procedure/Treatment MAY BE CONSIDERED</b> <ul style="list-style-type: none"> <li>• Recommendation's usefulness/efficacy less well established</li> <li>• Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<b>Benefit &lt; Risk</b> <b>Procedure/Treatment MAY BE CONSIDERED</b> <ul style="list-style-type: none"> <li>• Recommendation's usefulness/efficacy less well established</li> <li>• Greater conflicting evidence from single randomized trial or nonrandomized studies</li> <li>• Recommendation's usefulness/efficacy less well established</li> <li>• Only diverging expert opinion, case studies, or standard-of-care</li> </ul>
Level B Limited (2–3) population risk strata evaluated*	<ul style="list-style-type: none"> <li>• Recommendation that procedure or treatment is useful/effective</li> <li>• Limited evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>• Recommendation in favor of treatment or procedure being useful/effective</li> <li>• Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>• Recommendation in favor of treatment or procedure being useful/effective</li> <li>• Only diverging expert opinion, case studies, or standard-of-care</li> </ul>	
Level C Very limited (1–2) population risk strata evaluated*	<ul style="list-style-type: none"> <li>• Recommendation that procedure or treatment is useful/effective</li> <li>• Only expert opinion, case studies, or standard-of-care</li> </ul>	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear /uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful
<b>Suggested phrases for writing recommendations†</b>	should is recommended is indicated is useful/effective/beneficial			

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use.

†The ACC/AHA Task Force on Practice Guidelines recently provided a list of suggested phrases to use when writing recommendations. All recommendations in the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

- fear of potential embarrassment (*Level of Evidence: C*)
- d. A plan for appropriate recognition and response to a potential acute cardiac event that includes the phone number to access emergency medical services (EMS), generally 9-1-1.<sup>15</sup> (*Level of Evidence: C*)
  3. Healthcare providers should instruct patients for whom nitroglycerin has been prescribed previously to take ONE nitroglycerin dose sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or worsening 5 minutes after 1 sublingual nitroglycerin dose has been taken, it is recommended

that the patient or family member/friend call 9-1-1 immediately to access EMS. (*Level of Evidence: C*)

Morbidity and mortality due to STEMI can be reduced significantly if patients and bystanders recognize symptoms early, activate the EMS system, and thereby shorten the time to definitive treatment. Patients with possible symptoms of STEMI should be transported to the hospital by ambulance rather than by friends or relatives because there is a significant association between arrival at the emergency department (ED) by ambulance and early reperfusion therapy.<sup>16–19</sup> Although the traditional recommendation is for patients to take 1 nitroglycerin dose sublingually, 5 minutes apart, for up to 3 doses before

calling for emergency evaluation, this recommendation has been modified by the writing committee to encourage earlier contacting of EMS by patients with symptoms suggestive of STEMI.<sup>20,21</sup>

## IV. Onset of STEMI

### A. Out-of-Hospital Cardiac Arrest

#### *Class I*

1. All communities should create and maintain a strong "Chain of Survival" for out-of-hospital cardiac arrest that includes early access (recognition of the problem and activation of the EMS system by a bystander), early cardiopulmonary resuscitation (CPR), early defibrillation for patients who need it, and early advanced cardiac life support (ACLS). (*Level of Evidence: C*)
2. Family members of patients experiencing STEMI should be advised to take CPR training and familiarize themselves with the use of an automated external defibrillator (AED). In addition, they should be referred to a CPR training program that has a social support component for family members of post-STEMI patients. (*Level of Evidence: B*)

The links in the chain include early access (recognition of the problem and activation of the EMS system by a bystander), early CPR, early defibrillation for patients who need it, and early ACLS.

## V. Prehospital Issues

### A. Emergency Medical Services Systems

#### *Class I*

1. All EMS first responders who respond to patients with chest pain and/or suspected cardiac arrest should be trained and equipped to provide early defibrillation. (*Level of Evidence: A*)
2. All public safety first responders who respond to patients with chest pain and/or suspected cardiac arrest should be trained and equipped to provide early defibrillation with AEDs. (Provision of early defibrillation with AEDs by nonpublic safety first responders is a promising new strategy, but further study is needed to determine its safety and efficacy.) (*Level of Evidence: B*)
3. Dispatchers staffing 9-1-1 center emergency medical calls should have medical training, should use nationally developed and maintained protocols, and should have a quality-improvement system in place to ensure compliance with protocols. (*Level of Evidence: C*)

Early access to EMS is promoted by a 9-1-1 system currently available to more than 90% of the US population. To minimize time to treatment, particularly for cardiopulmonary arrest, many communities allow volunteer and/or paid firefighters and other first-aid providers to function as first responders, providing CPR and, increasingly, early defibrillation using automated external defibrillators (AEDs) until emergency medical technicians and paramedics arrive. Most cities and larger suburban areas provide EMS ambulance

services with providers from the fire department, a private ambulance company, and/or volunteers.

### B. Prehospital Chest Pain Evaluation and Treatment

#### *Class I*

1. Prehospital EMS providers should administer 162 to 325 mg of aspirin (chewed) to chest pain patients suspected of having STEMI unless contraindicated or already taken by patient. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. (*Level of Evidence: C*)

#### *Class IIa*

1. It is reasonable for all 9-1-1 dispatchers to advise patients without a history of aspirin allergy who have symptoms of STEMI to chew aspirin (162 to 325 mg) while awaiting arrival of prehospital EMS providers. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations. (*Level of Evidence: C*)
2. It is reasonable that all ACLS providers perform and evaluate 12-lead electrocardiograms (ECGs) routinely on chest pain patients suspected of STEMI. (*Level of Evidence: B*)
3. If the ECG shows evidence of STEMI, it is reasonable that prehospital ACLS providers review a reperfusion "checklist" and relay the ECG and checklist findings to a predetermined medical control facility and/or receiving hospital. (*Level of Evidence: C*)

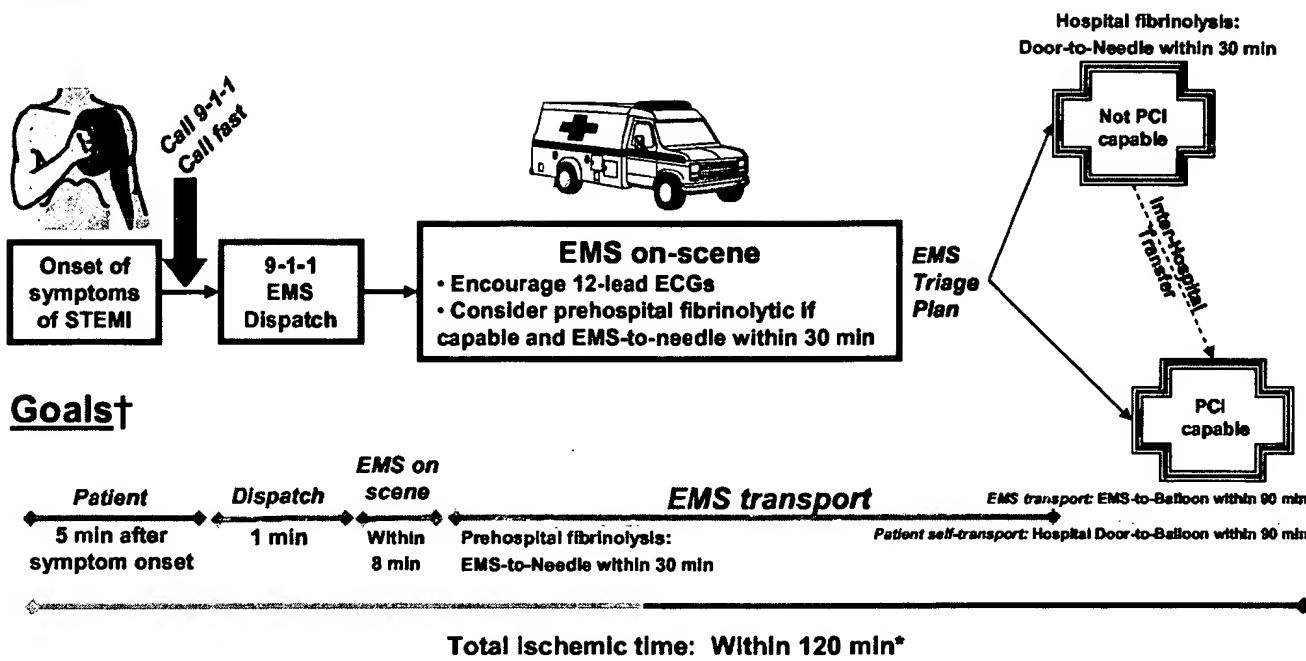
It is reasonable for physicians to encourage the prehospital administration of aspirin via EMS personnel (ie, EMS dispatchers and providers) in patients with symptoms suggestive of STEMI unless its use is contraindicated.<sup>22</sup> For patients who have ECG evidence of STEMI, it is reasonable that paramedics review a reperfusion checklist and relay the ECG and checklist findings to a predetermined medical control facility and/or receiving hospital.

### C. Prehospital Fibrinolysis

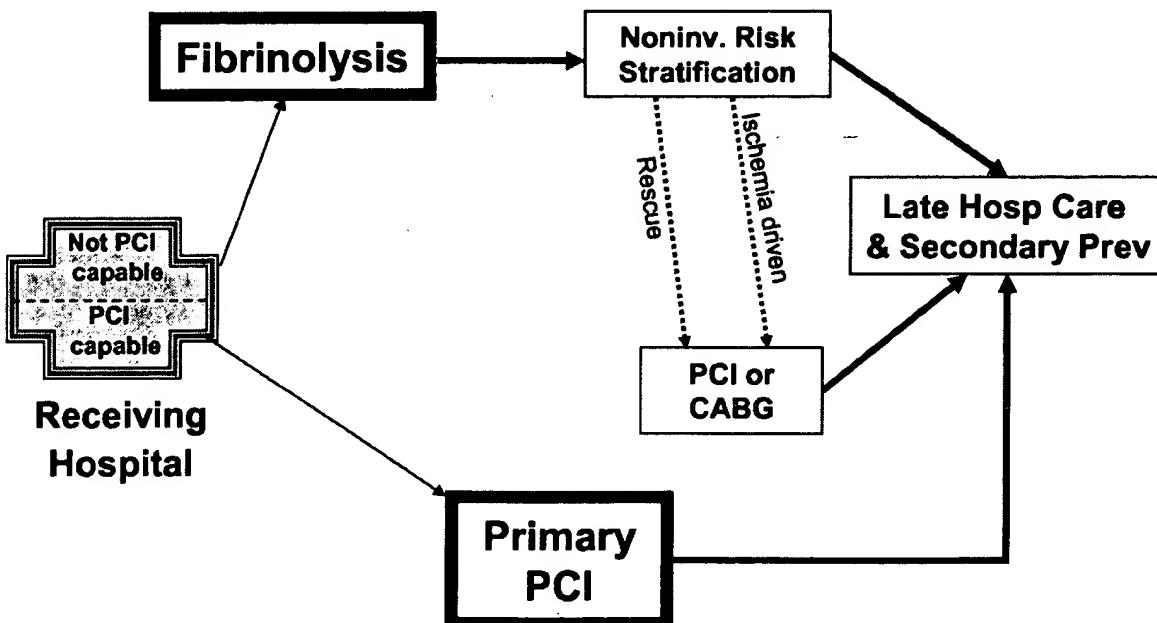
#### *Class IIa*

1. Establishment of a prehospital fibrinolysis protocol is reasonable in 1) settings in which physicians are present in the ambulance or in 2) well-organized EMS systems with full-time paramedics who have 12-lead ECGs in the field with transmission capability, paramedic initial and ongoing training in ECG interpretation and STEMI treatment, online medical command, a medical director with training/experience in STEMI management, and an ongoing continuous quality-improvement program. (*Level of Evidence: B*)

Randomized controlled trials of fibrinolytic therapy have demonstrated the benefit of initiating fibrinolytic therapy as early as possible after onset of ischemic-type chest discomfort (Figure 1).<sup>23-25</sup> It appears reasonable to expect that if

**Panel A**

\*Golden Hour = First 60 minutes

**Panel B**

**Figure 1.** Options for transportation of STEMI patients and initial reperfusion treatment. **Panel A,** Patient transported by EMS after calling 9-1-1: Reperfusion in patients with STEMI can be accomplished by the pharmacological (fibrinolysis) or catheter-based (primary PCI) approaches. Implementation of these strategies varies based on the mode of transportation of the patient and capabilities at the receiving hospital. Transport time to the hospital is variable from case to case, but the goal is to keep total ischemic time within 120 minutes. There are 3 possibilities: (1) If EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 minutes of EMS arrival on scene. (2) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a non-PCI-capable hospital, the hospital door-to-needle time should be within 30 minutes for patients in whom fibrinolysis is indicated. (3) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the hospital door-to-balloon time should be within 90 minutes. **Interhospital transfer:** It is also appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization if (1) there is a contraindication to fibrinolysis; (2) PCI can be initiated promptly

fibrinolytic therapy could be started at the time of prehospital evaluation, a greater number of lives could be saved. Prehospital fibrinolysis is reasonable in those settings in which physicians are present in the ambulance or prehospital transport times are more than 60 minutes in high-volume (more than 25,000 runs per year) EMS systems.<sup>26</sup> Other considerations for implementing a prehospital fibrinolytic service include the ability to transmit ECGs, paramedic initial and ongoing training in ECG interpretation and myocardial infarction (MI) treatment, online medical command, a medical director with training/experience in management of STEMI, and full-time paramedics.<sup>27</sup>

#### D. Prehospital Destination Protocols

##### *Class I*

1. Patients with STEMI who have cardiogenic shock and are less than 75 years of age should be brought immediately or secondarily transferred to facilities capable of cardiac catheterization and rapid revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) if it can be performed within 18 hours of onset of shock. (*Level of Evidence: A*)
2. Patients with STEMI who have contraindications to fibrinolytic therapy should be brought immediately or secondarily transferred promptly (ie, primary-receiving hospital door-to-departure time less than 30 minutes) to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). (*Level of Evidence: B*)
3. Every community should have a written protocol that guides EMS system personnel in determining where to

**Figure 1 (continued).** (within 90 minutes after the patient presented to the initial receiving hospital or within 60 minutes compared to when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital); or (3) fibrinolysis is administered and is unsuccessful (ie, "rescue PCI"). Secondary nonemergency interhospital transfer can be considered for recurrent ischemia. Patient self-transport: Patient self-transportation is discouraged. If the patient arrives at a non-PCI-capable hospital, the door-to-needle time should be within 30 minutes. If the patient arrives at a PCI-capable hospital, the door-to-balloon time should be within 90 minutes. The treatment options and time recommendations after first hospital arrival are the same. Panel B, For patients who receive fibrinolysis, noninvasive risk stratification is recommended to identify the need for rescue PCI (failed fibrinolysis) or ischemia-driven PCI. See Sections 6.3.1.6.4.5. and 6.3.1.6.7. in the full-text guidelines. Regardless of the initial method of reperfusion treatment, all patients should receive late hospital care and secondary prevention of STEMI. EMS indicates Emergency Medical System; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; Hosp, hospital; Noninv., Noninvasive. \*Golden hour = First 60 minutes;†The medical system goal is to facilitate rapid recognition and treatment of patients with STEMI such that door-to-needle (or medical contact-to-needle) time for initiation of fibrinolytic therapy is within 30 minutes or that door-to-balloon (or medical contact-to-balloon) time for PCI is within 90 minutes. These goals should not be understood as ideal times but rather as the longest times that should be considered acceptable for a given system. Systems that are able to achieve even more rapid times for treatment of patients with STEMI should be encouraged. Modified with permission from Armstrong et al. *Circulation.* 2003;107:2533–7.<sup>25</sup>

take patients with suspected or confirmed STEMI. (*Level of Evidence: C*)

##### *Class IIa*

1. It is reasonable that patients with STEMI who have cardiogenic shock and are 75 years of age or older be considered for immediate or prompt secondary transfer to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG) if it can be performed within 18 hours of onset of shock. (*Level of Evidence: B*)
2. It is reasonable that patients with STEMI who are at especially high risk of dying, including those with severe congestive heart failure (CHF), be considered for immediate or prompt secondary transfer (ie, primary-receiving hospital door-to-departure time less than 30 minutes) to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). (*Level of Evidence: B*)

Every community should have a written protocol that guides EMS system personnel in determining where to take patients with suspected or confirmed STEMI. Active involvement of local healthcare providers, particularly cardiologists and emergency physicians, is needed to formulate local EMS destination protocols for these patients. In general, patients with suspected STEMI should be taken to the nearest appropriate hospital. However, patients with STEMI and shock are an exception to this general rule. Whenever possible, STEMI patients less than 75 years of age with shock should be transferred to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG). On the basis of observations in the SHOCK Trial Registry and other registries, it is reasonable to extend such considerations of transfer to invasive centers for elderly patients with shock (see VII.F.5 and Section 7.6.5 of the full-text guidelines). Patients with STEMI who have contraindications to fibrinolytic therapy should be brought immediately or secondarily transferred promptly (ie, primary-receiving hospital door-to-departure time less than 30 minutes) to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG).

## VI. Initial Recognition and Management in the Emergency Department

#### A. Optimal Strategies for Emergency Department Triage

##### *Class I*

1. Hospitals should establish multidisciplinary teams (including primary care physicians, emergency medicine physicians, cardiologists, nurses, and laboratorians) to develop guideline-based, institution-specific written protocols for triaging and managing patients who are seen in the prehospital setting or present to the ED with symptoms suggestive of STEMI. (*Level of Evidence: B*)

#### B. Initial Patient Evaluation

##### *Class I*

1. The delay from patient contact with the healthcare system (typically, arrival at the ED or contact with

- paramedics) to initiation of fibrinolytic therapy should be less than 30 minutes. Alternatively, if PCI is chosen, the delay from patient contact with the healthcare system (typically, arrival at the ED or contact with paramedics) to balloon inflation should be less than 90 minutes. (*Level of Evidence: B*)
2. The choice of initial STEMI treatment should be made by the emergency medicine physician on duty based on a predetermined, institution-specific, written protocol that is a collaborative effort of cardiologists (both those involved in coronary care unit management and interventionalists), emergency physicians, primary care physicians, nurses, and other appropriate personnel. For cases in which the initial diagnosis and treatment plan is unclear to the emergency physician or is not covered directly by the agreed-on protocol, immediate cardiology consultation is advisable. (*Level of Evidence: C*)

Regardless of the approach used, all patients presenting to the ED with chest discomfort or other symptoms suggestive of STEMI or unstable angina should be considered high-priority triage cases and should be evaluated and treated based on a predetermined, institution-specific chest pain protocol. The goal for patients with STEMI should be to achieve a door-to-needle time within 30 minutes and a door-to-balloon time within 90 minutes (Figure 1).<sup>25</sup>

#### **1. History**

##### **Class I**

1. The targeted history of STEMI patients taken in the ED should ascertain whether the patient has had prior episodes of myocardial ischemia such as stable or unstable angina, MI, CABG, or PCI. Evaluation of the patient's complaints should focus on chest discomfort, associated symptoms, sex- and age-related differences in presentation, hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding, and clinical cerebrovascular disease (amaurosis fugax, face/limb weakness or clumsiness, face/limb numbness or sensory loss, ataxia, or vertigo). (*Level of Evidence: C*)

#### **2. Physical Examination**

##### **Class I**

1. A physical examination should be performed to aid in the diagnosis and assessment of the extent, location, and presence of complications of STEMI. (*Level of Evidence: C*)
2. A brief, focused, and limited neurological examination to look for evidence of prior stroke or cognitive deficits should be performed on STEMI patients before administration of fibrinolytic therapy. (*Level of Evidence: C*)

A brief physical examination may promote rapid triage, whereas a more detailed physical examination aids in the differential diagnosis and is useful for assessing the extent, location, and presence of complications of STEMI.

#### **3. Electrocardiogram**

##### **Class I**

1. A 12-lead ECG should be performed and shown to an experienced emergency physician within 10 minutes of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of STEMI. (*Level of Evidence: C*)
2. If the initial ECG is not diagnostic of STEMI but the patient remains symptomatic, and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous 12-lead ST-segment monitoring should be performed to detect the potential development of ST elevation. (*Level of Evidence: C*)
3. In patients with inferior STEMI, right-sided ECG leads should be obtained to screen for ST elevation suggestive of right ventricular (RV) infarction. (See Section 7.6.6 of the full-text guidelines and the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography.) (*Level of Evidence: B*)

The 12-lead ECG in the ED is at the center of the therapeutic decision pathway because of the strong evidence that ST-segment elevation identifies patients who benefit from reperfusion therapy.<sup>28</sup>

#### **4. Laboratory Examinations**

##### **Class I**

1. Laboratory examinations should be performed as part of the management of STEMI patients but should not delay the implementation of reperfusion therapy. (*Level of Evidence: C*)

In addition to serum cardiac biomarkers for cardiac damage, several routine evaluations have important implications for management of patients with STEMI. Although these studies should be ordered when the patient is first seen, therapeutic decisions should not be delayed until results are obtained because of the crucial role of time to therapy in STEMI.

#### **5. Biomarkers of Cardiac Damage**

##### **Class I**

1. Cardiac-specific troponins should be used as the optimum biomarkers for the evaluation of patients with STEMI who have coexistent skeletal muscle injury. (*Level of Evidence: C*)
2. For patients with ST elevation on the 12-lead ECG and symptoms of STEMI, reperfusion therapy should be initiated as soon as possible and is not contingent on a biomarker assay. (*Level of Evidence: C*)

##### **Class IIa**

1. Serial biomarker measurements can be useful to provide supportive noninvasive evidence of reperfusion of the infarct artery after fibrinolytic therapy in patients not undergoing angiography within the first 24 hours after fibrinolytic therapy. (*Level of Evidence: B*)

**Class III**

1. Serial biomarker measurements should not be relied on to diagnose reinfarction within the first 18 hours after the onset of STEMI. (*Level of Evidence: C*)

For patients with ST-segment elevation, the diagnosis of STEMI is secure; initiation of reperfusion therapy should not be delayed to wait for the results of a cardiac biomarker assay.<sup>29</sup> Quantitative analysis of cardiac biomarker measurements provides prognostic information and a noninvasive assessment of the likelihood that the patient has undergone successful reperfusion when fibrinolytic therapy is administered.

*a. Bedside Testing for Serum Cardiac Biomarkers***Class I**

1. Although handheld bedside (point-of-care) assays may be used for a qualitative assessment of the presence of an elevated level of a serum cardiac biomarker, subsequent measurements of cardiac biomarker levels should be performed with a quantitative test. (*Level of Evidence: B*)
2. For patients with ST elevation on the 12-lead ECG and symptoms of STEMI, reperfusion therapy should be initiated as soon as possible and is not contingent on a bedside biomarker assay. (*Level of Evidence: C*)

A positive bedside test should be confirmed by a conventional quantitative test. However, reperfusion therapy should not be delayed to wait for the results of a quantitative assay.

*6. Imaging***Class I**

1. Patients with STEMI should have a portable chest X-ray, but this should not delay implementation of reperfusion therapy (unless a potential contraindication, such as aortic dissection, is suspected). (*Level of Evidence: C*)
2. Imaging studies such as a high-quality portable chest X-ray, transthoracic and/or transesophageal echocardiography, and a contrast chest computed tomographic scan or a MRI scan should be used to differentiate STEMI from aortic dissection in patients for whom this distinction is initially unclear. (*Level of Evidence: B*)

**Class IIa**

1. Portable echocardiography is reasonable to clarify the diagnosis of STEMI and allow risk stratification of patients with chest pain on arrival at the ED, especially if the diagnosis of STEMI is confounded by left bundle-branch block (LBBB) or pacing, or there is suspicion of posterior STEMI with anterior ST depressions. (See Section 7.6.7 Mechanical Causes of Heart Failure/Low Output Syndrome of the full-text guidelines.) (*Level of Evidence: B*)

**Class III**

1. Single-photon emission computed tomography (SPECT) radionuclide imaging should not be performed to diagnose STEMI in patients for whom the diagnosis of STEMI is evident on the ECG. (*Level of Evidence: B*)

**C. Management***1. Routine Measures**a. Oxygen***Class I**

1. Supplemental oxygen should be administered to patients with arterial oxygen desaturation ( $\text{SaO}_2$  less than 90%). (*Level of Evidence: B*)

**Class IIa**

1. It is reasonable to administer supplemental oxygen to all patients with uncomplicated STEMI during the first 6 hours. (*Level of Evidence: C*)

*b. Nitroglycerin***Class I**

1. Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin. (*Level of Evidence: C*)
2. Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. (*Level of Evidence: C*)

**Class III**

1. Nitrates should not be administered to patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 bpm), tachycardia (more than 100 bpm), or suspected RV infarction. (*Level of Evidence: C*)
2. Nitrates should not be administered to patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (48 hours for tadalafil). (*Level of Evidence: B*)

Nitroglycerin may be administered to relieve ischemic pain and is clearly indicated as a vasodilator in patients with STEMI associated with left ventricular (LV) failure. Nitrates in all forms should be avoided in patients with initial systolic blood pressures less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, in patients with marked bradycardia or tachycardia,<sup>30</sup> and in patients with known or suspected RV infarction. In view of their marginal treatment benefits, nitrates should not be used if hypotension limits the administration of beta-blockers, which have more powerful salutary effects.

*c. Analgesia***Class I**

1. Morphine sulfate (2 to 4 mg IV with increments of 2 to 8 mg IV repeated at 5- to 15-minute intervals) is the analgesic of choice for management of pain associated with STEMI. (*Level of Evidence: C*)

*d. Aspirin**Class I*

- Aspirin should be chewed by patients who have not taken aspirin before presentation with STEMI. The initial dose should be 162 mg (*Level of Evidence: A*) to 325 mg (*Level of Evidence: C*). Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated aspirin formulations.**

In a dose of 162 mg or more, aspirin produces a rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A2 production. Aspirin now forms part of the early management of all patients with suspected STEMI and should be given promptly, and certainly within the first 24 hours, at a dose between 162 and 325 mg and continued indefinitely at a daily dose of 75 to 162 mg.<sup>31</sup> Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non-enteric-coated formulations.<sup>32</sup>

*e. Beta-Blockers**Class I*

- Oral beta-blocker therapy should be administered promptly to those patients without a contraindication, irrespective of concomitant fibrinolytic therapy or performance of primary PCI. (*Level of Evidence: A*)**

*Class IIa*

- It is reasonable to administer IV beta-blockers promptly to STEMI patients without contraindications, especially if a tachyarrhythmia or hypertension is present. (*Level of Evidence: B*)**

Immediate beta-blocker therapy appears to reduce the magnitude of infarction and incidence of associated complications in subjects not receiving concomitant fibrinolytic therapy, the rate of reinfarction in patients receiving fibrinolytic therapy, and the frequency of life-threatening ventricular tachyarrhythmias.

*f. Reperfusion*

## GENERAL CONCEPTS.

*Class I*

- All STEMI patients should undergo rapid evaluation for reperfusion therapy and have a reperfusion strategy implemented promptly after contact with the medical system. (*Level of Evidence: A*)**

Evidence exists that expeditious restoration of flow in the obstructed infarct artery after the onset of symptoms in STEMI patients is a key determinant of short- and long-term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or PCI.<sup>33-35</sup> As discussed previously (also see Section 4.1 of the full-text guidelines), efforts should be made to shorten the time from recognition of symptoms by the patient to contact with the medical system. All healthcare providers caring for STEMI patients from the point of entry into the medical system must recognize the need for rapid triage and implementation of care in a fashion analogous to the handling of trauma patients. When considering recommendations for timely reperfusion of STEMI patients, the Writing Committee

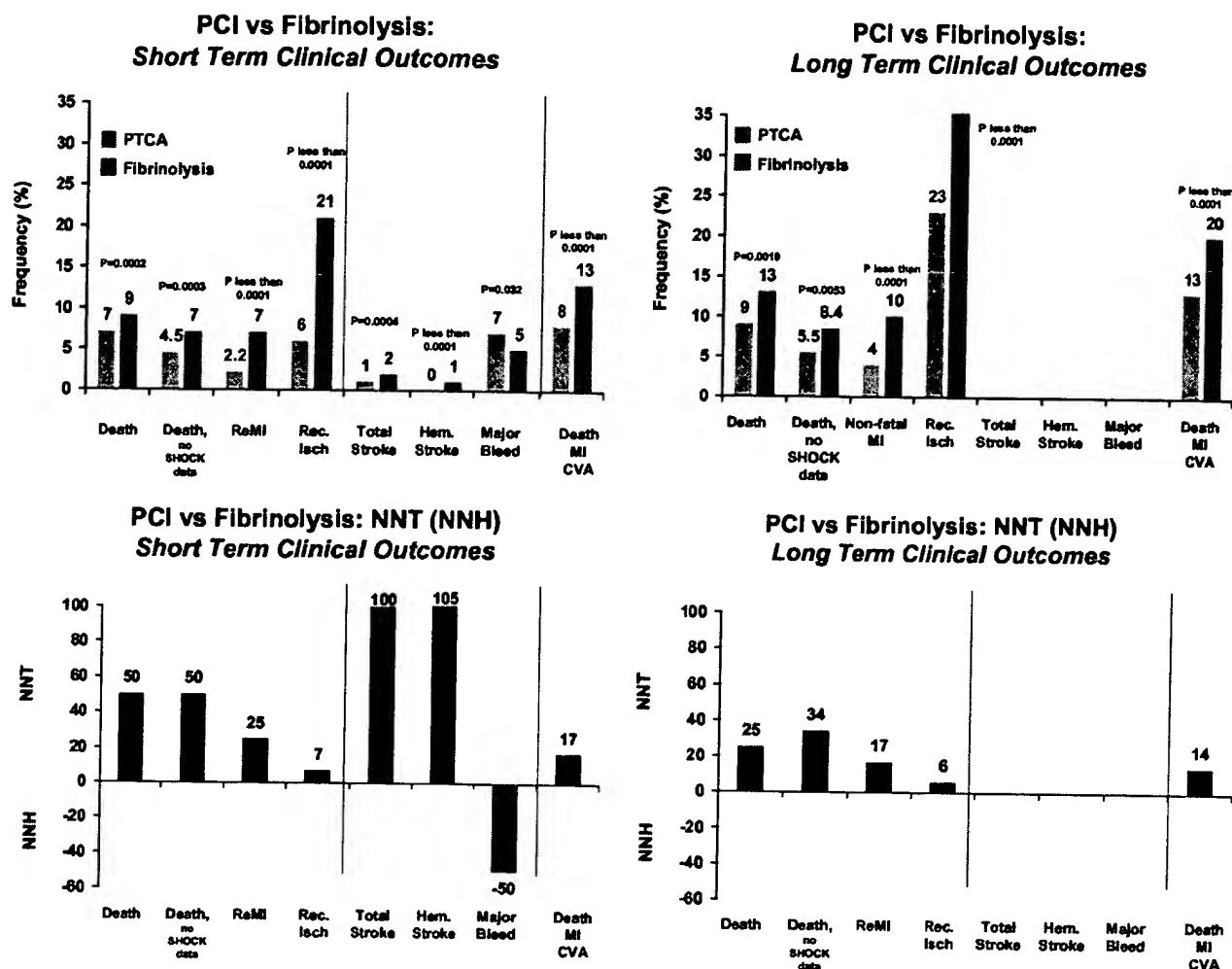
reviewed data from clinical trials, focusing particular attention on enrollment criteria for selection of patients for randomization, actual times reported in the trial report rather than simply the allowable window specified in the trial protocol, treatment effect of the reperfusion strategy on individual components of a composite primary end point (eg, mortality, recurrent nonfatal infarction), ancillary therapies (eg, antithrombin and antiplatelet agents), and the interface between fibrinolysis and referral for angiography and revascularization. When available, data from registries were also reviewed to assess the generalizability of observations from clinical trials of reperfusion to routine practice. Despite the wealth of reports on reperfusion for STEMI, it is not possible to produce a simple algorithm, given the heterogeneity of patient profiles and availability of resources in various clinical settings at various times of day. This section introduces the recommendations for an aggressive attempt to minimize the time from entry into the medical system to implementation of a reperfusion strategy using the concept of medical system goals. More detailed discussion of these goals and the issues to be considered in selecting the type of reperfusion therapy are discussed in the Selection of Reperfusion Therapy section of VI.C.1.f (Section 6.3.1.6.2 of the full-text guidelines), followed by a discussion of available resources.

The medical system goal is to facilitate rapid recognition and treatment of patients with STEMI such that door-to-needle (or medical contact-to-needle) time for initiation of fibrinolytic therapy can be achieved within 30 minutes or that door-to-balloon (or medical contact-to-balloon) time for PCI can be kept under 90 minutes. These goals may not be relevant for the patients with an appropriate reason for delay, such as uncertainty about the diagnosis (particularly for the use of fibrinolytic therapy), need for the evaluation and treatment of other life-threatening conditions (eg, respiratory failure), or delays associated with the patient's informed choice to have more time to consider the decision. In the absence of such types of circumstances, the emphasis is on having a system in place such that when a patient with STEMI presents for medical care, reperfusion therapy is able to be provided as soon as possible within these time periods. Because there is not considered to be a threshold effect for the benefit of shorter times to reperfusion, these goals should not be understood as "ideal" times but the longest times that should be considered acceptable. Systems that are able to achieve even more rapid times for patients should be encouraged. Also, this goal should not be perceived as an average performance standard but a goal of an early treatment system that every hospital should seek for every appropriate patient.

## SELECTION OF REPERFUSION STRATEGY. Several issues should be considered in selecting the type of reperfusion therapy:

- Time From Onset of Symptoms.** Time from onset of symptoms to fibrinolytic therapy is an important predictor of MI size and patient outcome.<sup>36</sup> The efficacy of fibrinolytic agents in lysing thrombus diminishes with the passage of time.<sup>37</sup> Fibrinolytic therapy administered within the first 2 hours (especially the first hour) can occasionally abort MI and dramatically reduce mortality.<sup>23,38</sup>

In contrast, the ability to produce a patent infarct artery is much less dependent on symptom duration in patients undergoing PCI. Several reports claim no influence of time delay on mortality rates when PCI is performed after 2 to 3 hours of symptom duration.<sup>39,40</sup> Importantly, after adjust-



**Figure 2.** PCI vs fibrinolysis for STEMI. Short-term (4 to 6 weeks; top left) and long-term (top right) outcomes for various end points shown are plotted for STEMI patients randomized to PCI or fibrinolysis for reperfusion in 23 trials ( $n=7739$ ). Given the frequency of events for each end point in the 2 treatment groups, the number needed to treat (NNT) or number needed to harm (NNH) is shown for the short-term (bottom left) and long-term (bottom right) outcomes. The magnitude of treatment differences for death, nonfatal reinfarction, and stroke varies depending on whether PCI is compared with streptokinase or a fibrin-specific lytic. For example, when primary PCI is compared with alteplase and the SHOCK trial is excluded, the mortality rate is 5.5% vs 6.7% (odds ratio 0.81, 95% confidence interval 0.64 to 1.03,  $P=0.081$ ).<sup>76a</sup> See references 76 and 76a for additional discussion. Modified with permission from Elsevier (Keeley et al. *The Lancet*. 2003;361:13–20).<sup>76</sup> ReMI indicates recurrent MI; Rec. Isch, recurrent ischemia; Hem. Stroke, hemorrhagic stroke; and CVA, cerebrovascular accident.

ment for baseline characteristics, time from symptom onset to balloon inflation is significantly correlated with 1-year mortality in patients undergoing primary PCI for STEMI.<sup>41</sup> The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology<sup>42</sup> and this Committee both recommend a target of medical contact-to-balloon or door-to-balloon time within 90 minutes.

- **Risk of STEMI.** Several models have been developed that assist clinicians in estimating the risk of mortality in patients with STEMI.<sup>43–47</sup> Although these models vary somewhat in the factors loaded into the risk-prediction tool and also vary with respect to statistical measures of their discriminative power (eg, C statistic), all the models provide clinicians with a means to assess the continuum of risk from STEMI. When the estimated mortality with fibrinolysis is extremely high, as is the case in patients with cardiogenic shock, compelling evidence exists that favors a PCI strategy.

- **Risk of Bleeding.** Choice of reperfusion therapy is also affected by the patient's risk of bleeding. When both types of reperfusion are available, the higher the patient's risk of bleeding with fibrinolytic therapy, the more strongly the decision should favor PCI. If PCI is unavailable, then the benefit of pharmacological reperfusion therapy should be balanced against the risk.
- **Time Required for Transport to a Skilled PCI Laboratory.** The availability of interventional cardiology facilities is a key determinant of whether PCI can be provided. For facilities that can offer PCI, the literature suggests that this approach is superior to pharmacological reperfusion.<sup>48</sup> The trials comparing pharmacological and PCI strategies, however, were conducted before the advent of more recent pharmacological and PCI strategies. When a composite end point of death, nonfatal recurrent MI, or stroke is analyzed, much of the superiority of a PCI strategy is driven by a reduction in the rate of nonfatal recurrent MI (Figure 2).<sup>36</sup>

**STEP 1: Assess Time and Risk**

- Time since onset of symptoms
- Risk of STEMI
- Risk of fibrinolysis
- Time required for transport to a skilled PCI laboratory

**STEP 2: Determine Whether Fibrinolysis or an Invasive Strategy Is Preferred**

*If presentation is less than 3 hours and there is no delay to an invasive strategy, there is no preference for either strategy.*

<p><b>Fibrinolysis is generally preferred if (see Section 6.3.1.6.3.1 of the full-text guidelines):</b></p> <ul style="list-style-type: none"> <li>▪ <i>Early presentation (3 hours or less from symptom onset and delay to invasive strategy; see below)</i></li> <li>▪ <i>Invasive strategy is not an option</i> <ul style="list-style-type: none"> <li>Catheterization laboratory occupied/not available</li> <li>Vascular access difficulties</li> <li>Lack of access to a skilled PCI laboratory††</li> </ul> </li> <li>▪ <i>Delay to invasive strategy</i> <ul style="list-style-type: none"> <li>Prolonged transport</li> <li>(Door-to-Balloon) – (Door-to-Needle) time is greater than 1 hour§</li> <li>Medical contact–to-balloon or door-to-balloon time is greater than 90 minutes</li> </ul> </li> </ul>	<p><b>An invasive strategy is generally preferred if (see Section 6.3.1.6.4.2 of the full-text guidelines):</b></p> <ul style="list-style-type: none"> <li>▪ <i>Skilled PCI laboratory available with surgical backup ††</i> <ul style="list-style-type: none"> <li>Medical contact–to-balloon or door-to-balloon time less than 90 minutes</li> <li>(Door-to-Balloon) – (Door-to-Needle) is less than 1 hour*</li> </ul> </li> <li>▪ <i>High risk from STEMI</i> <ul style="list-style-type: none"> <li>Cardiogenic shock</li> <li>Killip class greater than or equal to 3</li> </ul> </li> <li>▪ <i>Contraindications to fibrinolysis, including increased risk of bleeding and ICH</i></li> <li>▪ <i>Late presentation</i> <ul style="list-style-type: none"> <li>Symptom onset was more than 3 hours ago</li> </ul> </li> <li>▪ <i>Diagnosis of STEMI is in doubt</i></li> </ul>
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**Figure 3.** Assessment of reperfusion options for patients with STEMI. STEMI indicates ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; ICH, intracranial hemorrhage. \*Applies to fibrin-specific agents (see Figure 15 in the full-text STEMI guidelines). †Operator experience greater than a total of 75 primary PCI cases per year. ‡Team experience greater than a total of 36 primary PCI cases per year. §This calculation implies that the estimated delay to the implementation of the invasive strategy is greater than 1 hour vs initiation of fibrinolytic therapy immediately with a fibrin-specific agent.

The rate of nonfatal recurrent MI can be influenced both by the adjunctive therapy used and by the proportion of patients who are referred for PCI when the initial attempt at fibrinolysis fails or myocardial ischemia recurs after initially successful pharmacological reperfusion.

The experience and location of the PCI laboratory also plays a role in the choice of therapy. Not all laboratories can provide prompt, high-quality primary PCI. Even centers with interventional cardiology facilities may not be able to provide the staffing required for 24-hour coverage of the catheterization laboratory. Despite staffing availability, the volume of cases in the laboratory may be insufficient for the team to acquire and maintain skills required for rapid PCI reperfusion strategies.

A decision must be made when a STEMI patient presents to a center without interventional cardiology facilities. Fibrinolytic therapy can generally be provided sooner than primary PCI. As the time delay for performing PCI increases, the mortality benefit associated with expeditiously performed primary PCI over fibrinolysis decreases.<sup>49</sup> Compared with a fibrin-specific lytic agent, a PCI strategy may not reduce mortality when a delay greater than 60 minutes is anticipated versus immediate administration of a lytic.

Given the current literature, it is not possible to say definitively that a particular reperfusion approach is superior for all patients, in all clinical settings, at all times of day (Danchin N; oral presentation at American Heart Association Scientific Ses-

sions 2003, Orlando, FL, November 2003).<sup>50–52</sup> The main point is that some type of reperfusion therapy should be selected for all appropriate patients with suspected STEMI. The appropriate and timely use of some reperfusion therapy is likely more important than the choice of therapy, given the current literature and the expanding array of options. Clinical circumstances in which fibrinolytic therapy is generally preferred or an invasive strategy is generally preferred are shown in Figure 3.

#### Available Resources

##### **Class I**

1. STEMI patients presenting to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact should undergo fibrinolysis unless contraindicated. (*Level of Evidence: A*)

#### PHARMACOLOGICAL REPERFUSION.

##### Indications for Fibrinolytic Therapy

##### **Class I**

1. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads. (*Level of Evidence: A*)

- 2. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB. (Level of Evidence: A)**

#### **Class IIa**

- 1. In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to STEMI patients with symptom onset within the prior 12 hours and 12-lead ECG findings consistent with a true posterior MI. (Level of Evidence: C)**
- 2. In the absence of contraindications, it is reasonable to administer fibrinolytic therapy to patients with symptoms of STEMI beginning within the prior 12 to 24 hours who have continuing ischemic symptoms and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads. (Level of Evidence: B)**

#### **Class III**

- 1. Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began more than 24 hours earlier. (Level of Evidence: C)**
- 2. Fibrinolytic therapy should not be administered to patients whose 12-lead ECG shows only ST-segment depression except if a true posterior MI is suspected. (Level of Evidence: A)**

Because the benefit of fibrinolytic therapy is directly related to the time from symptom onset, treatment benefit is maximized by the earliest possible application of therapy. The constellation of clinical features that must be present (although not necessarily at the same time) to serve as an indication for fibrinolysis includes symptoms of myocardial ischemia and ST elevation greater than 0.1 mV, in at least 2 contiguous leads, or new or presumably new LBBB on the presenting ECG.<sup>23,54</sup>

#### Contraindications/Cautions

##### **Class I**

- 1. Healthcare providers should ascertain whether the patient has neurological contraindications to fibrinolytic therapy, including any history of intracranial hemorrhage (ICH), significant closed head or facial trauma within the past 3 months, uncontrolled hypertension, or ischemic stroke within the past 3 months. (See Table 2 for a comprehensive list.) (Level of Evidence: A)**
- 2. STEMI patients at substantial (greater than or equal to 4%) risk of ICH should be treated with PCI rather than with fibrinolytic therapy. (See Figure 3 for further management considerations.) (Level of Evidence: A)**

A detailed list of contraindications and cautions for the use of fibrinolytic therapy is shown in Table 2.

#### Complications of Fibrinolytic Therapy: Neurological and Other

##### **Class I**

- 1. The occurrence of a change in neurological status during or after reperfusion therapy, particularly**

**TABLE 2. Contraindications and Cautions for Fibrinolysis Use in ST-Elevation Myocardial Infarction\***

#### Absolute contraindications

- Any prior ICH
- Known structural cerebral vascular lesion (eg, AVM)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 months

#### Relative contraindications

- History of chronic severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP greater than 180 mm Hg or DBP greater than 110 mm Hg)†
- History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

AVM indicates arteriovenous malformation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICH, intracranial hemorrhage; CPR, cardiopulmonary resuscitation.

\*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.

†Could be an absolute contraindication in low-risk patients with ST-elevation myocardial infarction (see Section 6.3.1.6.3.2 of the full-text guidelines).

within the first 24 hours after initiation of treatment, is considered to be due to ICH until proven otherwise. Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until brain imaging scan shows no evidence of ICH. (Level of Evidence: A)

- 2. Neurology and/or neurosurgery or hematology consultations should be obtained for STEMI patients who have ICH as dictated by clinical circumstances. (Level of Evidence: C)**
- 3. In patients with ICH, infusions of cryoprecipitate, fresh frozen plasma, protamine, and platelets should be given, as dictated by clinical circumstances. (Level of Evidence: C)**

#### **Class IIa**

- 1. In patients with ICH, it is reasonable to:**
  - a. Optimize blood pressure and blood glucose levels. (Level of Evidence: C)**
  - b. Reduce intracranial pressure with an infusion of mannitol, endotracheal intubation, and hyperventilation. (Level of Evidence: C)**
  - c. Consider neurosurgical evacuation of ICH. (Level of Evidence: C)**

## Combination Therapy With Glycoprotein IIb/IIIa Inhibitors

**Class IIb**

1. Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction (*Level of Evidence: A*) and other complications of STEMI in selected patients: anterior location of MI, age less than 75 years, and no risk factors for bleeding. In two clinical trials of combination reperfusion, the prevention of reinfarction did not translate into a survival benefit at either 30 days or 1 year.<sup>54a</sup> (*Level of Evidence: B*)
2. Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction and other complications of STEMI in selected patients (anterior location of MI, age less than 75 years, and no risk factors for bleeding) in whom an early referral for angiography and PCI (ie, facilitated PCI) is planned. (*Level of Evidence: C*)

**Class III**

1. Combination pharmacological reperfusion with abciximab and half-dose reteplase or tenecteplase should not be given to patients aged greater than 75 years because of an increased risk of ICH. (*Level of Evidence: B*)

## PERCUTANEOUS CORONARY INTERVENTION

## Coronary Angiography

**Class I**

1. Diagnostic coronary angiography should be performed:
  - a. In candidates for primary or rescue PCI. (*Level of Evidence: A*)
  - b. In patients with cardiogenic shock who are candidates for revascularization. (*Level of Evidence: A*)
  - c. In candidates for surgical repair of ventricular septal rupture or severe mitral regurgitation (MR). (*Level of Evidence: B*)
  - d. In patients with persistent hemodynamic and/or electrical instability. (*Level of Evidence: C*)

**Class III**

1. Coronary angiography should not be performed in patients with extensive comorbidities in whom the risks of revascularization are likely to outweigh the benefits. (*Level of Evidence: C*)

## Primary PCI

**Class I**

1. General considerations: If immediately available, primary PCI should be performed in patients with STEMI (including true posterior MI) or MI with new or presumably new LBBB who can undergo PCI of the infarct artery within 12 hours of symptom onset, if performed in a timely fashion (balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (individuals who perform more than 75 PCI procedures per year). The procedure should be sup-

ported by experienced personnel in an appropriate laboratory environment (performs more than 200 PCI procedures per year, of which at least 36 are primary PCI for STEMI, and has cardiac surgery capability). (*Level of Evidence: A*)

**2. Specific considerations:**

- a. Primary PCI should be performed as quickly as possible, with a goal of a medical contact-to-balloon or door-to-balloon time of within 90 minutes. (*Level of Evidence: B*)
- b. If the symptom duration is within 3 hours and the expected door-to-balloon time minus the expected door-to-needle time is:
  - i) within 1 hour, primary PCI is generally preferred. (*Level of Evidence: B*)
  - ii) greater than 1 hour, fibrinolytic therapy (fibrin-specific agents) is generally preferred. (*Level of Evidence: B*)
- c. If symptom duration is greater than 3 hours, primary PCI is generally preferred and should be performed with a medical contact-to-balloon or door-to-balloon time as brief as possible, with a goal of within 90 minutes. (*Level of Evidence: B*)
- d. Primary PCI should be performed for patients younger than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: A*)
- e. Primary PCI should be performed in patients with severe CHF and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours. The medical contact-to-balloon or door-to-balloon time should be as short as possible (ie, goal within 90 min). (*Level of Evidence: B*)

**Class IIa**

1. Primary PCI is reasonable for selected patients 75 years or older with ST elevation or LBBB or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. (*Level of Evidence: B*)
2. It is reasonable to perform primary PCI for patients with onset of symptoms within the prior 12 to 24 hours and 1 or more of the following:
  - a. Severe CHF (*Level of Evidence: C*)
  - b. Hemodynamic or electrical instability (*Level of Evidence: C*)
  - c. Persistent ischemic symptoms. (*Level of Evidence: C*)

**Class IIb**

1. The benefit of primary PCI for STEMI patients eligible for fibrinolysis is not well established when per-

formed by an operator who performs fewer than 75 PCI procedures per year. (*Level of Evidence: C*)

### **Class III**

1. PCI should not be performed in a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise. (*Level of Evidence: C*)
2. Primary PCI should not be performed in asymptomatic patients more than 12 hours after onset of STEMI if they are hemodynamically and electrically stable. (*Level of Evidence: C*)

Primary PCI has been compared with fibrinolytic therapy in 22 randomized clinical trials.<sup>50,52,55-74</sup> An additional trial, SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK?),<sup>75</sup> that compared medical stabilization with immediate revascularization for cardiogenic shock was included along with the above 22 trials in an overview of primary PCI versus fibrinolysis.<sup>76</sup> These investigations demonstrate that PCI-treated patients experience lower short-term mortality rates, less nonfatal reinfarction, and less hemorrhagic stroke than those treated by fibrinolysis but have an increased risk for major bleeding.<sup>76</sup> These results have been achieved in medical centers with experienced providers and under circumstances in which PCI can be performed promptly after patient presentation (Figure 2).<sup>76</sup>

Additional considerations that affect the magnitude of the difference between PCI- and fibrinolysis-treated patients include the fact that unfractionated heparin (UFH) was used as the antithrombin with fibrinolitics (as opposed to other antithrombins such as enoxaparin [see Ancillary Therapy in Section VI.C.1.f and also Section 6.3.1.6.8.1.1 of the full-text guidelines] or bivalirudin [see Section 6.3.1.6.8.1.2 of the full-text guidelines] that are associated with a reduction in the rate of recurrent MI after fibrinolysis), a smaller but still statistically significant advantage for PCI compared with a fibrin-specific lytic versus streptokinase, and variation among the PCI arms as to whether a stent was implanted or glycoprotein (GP) IIb/IIIa antagonists were administered. Figure 2 shows the short- and long-term outcomes of patients with STEMI treated by fibrinolysis versus PCI and the number of patients who need to be treated to prevent 1 event or cause 1 harmful complication when selecting PCI instead of fibrinolysis as the reperfusion strategy (Figure 2).<sup>76</sup> Of note, when primary PCI is compared with tissue plasminogen activator (tPA) and the SHOCK trial is excluded, the mortality rate is 5.5% versus 6.7% (odds ratio 0.81%, 95% confidence interval [CI] 0.64 to 1.03, *P* equals 0.081).<sup>76a</sup>

There is serious and legitimate concern that a routine policy of primary PCI for patients with STEMI will result in unacceptable delays in achieving reperfusion in a substantial number of cases and produce less than optimal outcomes if performed by less-experienced operators. The mean time delay for PCI instead of fibrinolysis in the randomized studies was approximately 40 minutes.<sup>76</sup> Strict performance criteria must be mandated for primary PCI programs so that long door-to-balloon times and performance by low-volume or poor-outcome operators/laboratories do not occur. Interventional cardiologists and centers should strive for outcomes to include (1)

medical contact-to-balloon or door-to-balloon times less than 90 minutes; (2) TIMI (Thrombolysis In Myocardial Infarction) 2/3 flow rates obtained in more than 90% of patients; (3) emergency CABG rate less than 2% among all patients undergoing the procedure; (4) actual performance of PCI in a high percentage of patients (85%) brought to the laboratory; and (5) risk-adjusted in-hospital mortality rate less than 7% in patients without cardiogenic shock. This would result in a risk-adjusted mortality rate with PCI comparable to that reported for fibrinolytic therapy in fibrinolytic-eligible patients<sup>76</sup> and would be consistent with previously reported registry experience.<sup>77-80</sup> Otherwise, the focus of treatment should be the early use of fibrinolytic therapy (Figure 2).<sup>76</sup>

PCI appears to have its greatest mortality benefit in high-risk patients. In patients with cardiogenic shock, an absolute 9% reduction in 30-day mortality with coronary revascularization instead of immediate medical stabilization was reported in the SHOCK trial.<sup>75</sup>

Time from symptom onset to reperfusion is an important predictor of patient outcome. Two studies<sup>81,82</sup> have reported increasing mortality rates with increasing door-to-balloon times. Other studies have shown smaller infarct size, better LV function, and fewer complications when reperfusion occurs before PCI.<sup>83-85</sup> An analysis of the randomized controlled trials comparing fibrinolysis with a fibrin-specific agent versus primary PCI suggests that the mortality benefit with PCI exists when treatment is delayed by no more than 60 minutes. Mortality increases significantly with each 15-minute delay in the time between arrival and restoration of TIMI-3 flow (door-to-TIMI-3 flow time), which further underscores the importance of timely reperfusion in patients who undergo primary PCI.<sup>86</sup> Importantly, after adjustment for baseline characteristics, time from symptom onset to balloon inflation is significantly correlated with 1-year mortality in patients undergoing primary PCI for STEMI (relative risk equals 1.08 for each 30-minute delay from symptom onset to balloon inflation; *P* equals 0.04).<sup>35,41</sup> Given that the medical contact-to-needle time goal within 30 minutes, this Writing Committee joins the Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology in lowering the medical contact-to-balloon or door-to-balloon time goal from within 120 minutes to within 90 minutes in an attempt to maximize the benefits for reperfusion by PCI.<sup>42</sup>

If the expected door-to-balloon time exceeds the expected door-to-needle time by more than 60 minutes, fibrinolytic treatment with a fibrin-specific agent should be considered unless it is contraindicated. This is particularly important when symptom duration is less than 3 hours but is less important with longer symptom duration, when less ischemic myocardium can be salvaged.

### **PRIMARY PCI IN FIBRINOLYTIC-INELIGIBLE PATIENTS**

#### **Class I**

1. Primary PCI should be performed in fibrinolytic-ineligible patients who present with STEMI within 12 hours of symptom onset. (*Level of Evidence: C*)

#### **Class IIa**

1. It is reasonable to perform primary PCI for fibrinolytic-ineligible patients with onset of symptoms

**within the prior 12 to 24 hours and 1 or more of the following:**

- a. Severe CHF (*Level of Evidence: C*)
- b. Hemodynamic or electrical instability (*Level of Evidence: C*)
- c. Persistent ischemic symptoms. (*Level of Evidence: C*)

Randomized controlled trials evaluating the outcome of PCI for patients who present with STEMI but who are ineligible for fibrinolytic therapy have not been performed. Few data are available to characterize the value of primary PCI for this subset of STEMI patients; however, the recommendations in Section IV.A (and Section 4.2 of the full-text guidelines) are applicable to these patients. Nevertheless, these patients are at increased risk for mortality,<sup>87</sup> and there is a general consensus that PCI is an appropriate means for achieving reperfusion in those who cannot receive fibrinolysis because of increased risk of bleeding.<sup>88-91</sup>

#### *PRIMARY PCI WITHOUT ON-SITE CARDIAC SURGERY*

##### *Class IIb*

1. Primary PCI might be considered in hospitals without on-site cardiac surgery, provided that there exists a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital with appropriate hemodynamic support capability for transfer. The procedure should be limited to patients with STEMI or MI with new, or presumably new, LBBB on ECG, and should be done in a timely fashion (balloon inflation within 90 minutes of presentation) by persons skilled in the procedure (at least 75 PCIs per year) and at hospitals that perform a minimum of 36 primary PCI procedures per year. (*Level of Evidence: B*)

##### *Class III*

1. Primary PCI should not be performed in hospitals without on-site cardiac surgery and without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer. (*Level of Evidence: C*)

From clinical data and expert consensus, the Committee recommends that primary PCI for acute STEMI performed at hospitals without established elective PCI programs should be restricted to those institutions capable of performing a requisite minimum number of primary PCI procedures (36 per year) with a proven plan for rapid and effective PCI and rapid access to cardiac surgery in a nearby hospital. The benefit of primary PCI is not well established for operators who perform fewer than 75 PCIs per year or in a hospital that performs fewer than 36 primary PCI procedures per year. In addition, the benefit of timely reperfusion of the infarct artery by primary PCI at sites without on-site surgery must be weighed against the small but finite risk of harm to the patient related to the time required to transfer the patient to a site with CABG surgery capabilities.<sup>92,93</sup>

#### *INTERHOSPITAL TRANSFER FOR PRIMARY PCI*

To achieve optimal results, time from the first hospital door to the balloon inflation in the second hospital should

be as short as possible, with a goal of within 90 minutes. Significant reductions in door-to-balloon times might be achieved by directly transporting patients to PCI centers rather than transporting them to the nearest hospital, if interhospital transfer will subsequently be required to obtain primary PCI.

##### *Primary Stenting*

Primary stenting has been compared with primary angioplasty in 9 studies.<sup>94-103</sup> There were no differences in mortality (3.0% versus 2.8%) or reinfarction (1.8% versus 2.1%) rates. However, major adverse cardiac events were reduced, driven by the reduction in subsequent target-vessel revascularization with stenting.

Preliminary reports suggest that compared with conventional bare metal stents, drug-eluting stents are not associated with increased risk when used for primary PCI in STEMI patients.<sup>104</sup> Postprocedure vessel patency, biomarker release, and the incidence of short-term adverse events were similar in patients receiving sirolimus (n equals 186) or bare metal (n equals 183) stents. Thirty-day event rates of death, reinfarction, or revascularization were 7.5% versus 10.4%, respectively (*P* equals 0.4).<sup>104</sup>

##### *Facilitated PCI*

##### *Class IIb*

1. Facilitated PCI might be performed as a reperfusion strategy in higher-risk patients when PCI is not immediately available and bleeding risk is low. (*Level of Evidence: B*)

Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacological regimen such as full-dose fibrinolysis, half-dose fibrinolysis, a GP IIb/IIIa inhibitor, or a combination of reduced-dose fibrinolytic therapy and a platelet GP IIb/IIIa inhibitor. A strategy of facilitated PCI holds promise in higher-risk patients when PCI is not immediately available. Potential risks include increased bleeding complications, especially in patients who are at least 75 years of age (see Pharmacological Reperfusion in Section VI.C.1.f and Section 6.3.1.6.3.8. of the full-text guidelines), and potential limitations include added cost. Several randomized trials of facilitated PCI with a variety of pharmacological regimens are in progress.

##### *Rescue PCI*

##### *Class I*

1. Rescue PCI should be performed in patients less than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: B*)
2. Rescue PCI should be performed in patients with severe CHF and/or pulmonary edema (Killip class 3) and onset of symptoms within 12 hours. (*Level of Evidence: B*)

**Class IIa**

1. Rescue PCI is reasonable for selected patients 75 years or older with ST elevation or LBBB or who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. (*Level of Evidence: B*)
2. It is reasonable to perform rescue PCI for patients with 1 or more of the following:
  - a. Hemodynamic or electrical instability (*Level of Evidence: C*)
  - b. Persistent ischemic symptoms. (*Level of Evidence: C*)

Rescue PCI refers to PCI within 12 hours after failed fibrinolysis for patients with continuing or recurrent myocardial ischemia.

A major problem in adopting a strategy of rescue PCI lies in the limitation of accurate identification of patients for whom fibrinolytic therapy has not restored antegrade coronary flow. In a prior era in which the practice of PCI was less mature, immediate catheterization of all patients after fibrinolytic therapy to identify those with an occluded infarct artery was found to be impractical, costly, and often associated with bleeding complications.<sup>105,106</sup> This strategy is being re-evaluated in clinical trials testing facilitated PCI in the contemporary PCI setting.

There are no convincing data to support the routine use of late adjuvant PCI days after failed fibrinolysis or for patients who do not receive reperfusion therapy. Nevertheless, this is being done in some STEMI patients as an extension of the invasive strategy for non-STEMI patients. The Occluded Artery Trial (OAT) is currently randomizing patients to test whether routine PCI days to weeks after MI improves long-term clinical outcomes in asymptomatic high-risk patients with an occluded infarct artery.<sup>107</sup>

**PCI for Cardiogenic Shock****Class I**

1. Primary PCI is recommended for patients less than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: A*)

**Class IIa**

1. Primary PCI is reasonable for selected patients aged 75 years or older with ST elevation or LBBB who develop shock within 36 hours of MI and who are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization and agree to invasive care may be selected for such an invasive strategy. (*Level of Evidence: B*)

Observational studies support the value of PCI for patients who develop cardiogenic shock in the early hours of STEMI. In

the SHOCK trial,<sup>75</sup> the survival curves continued to progressively diverge such that at 6 months and 1 year, there was a significant mortality reduction with emergency revascularization (53% versus 66%, *P* less than 0.03).<sup>108</sup> The prespecified subgroup analysis of patients less than 75 years old showed an absolute 15% reduction in 30-day mortality (*P* less than 0.02), whereas there was no apparent benefit for the small cohort (*n* equals 56) of patients more than 75 years old. These data strongly support the approach that patients younger than 75 years with STEMI complicated by cardiogenic shock should undergo emergency revascularization and support measures. Three registries<sup>109-111</sup> have demonstrated a marked survival benefit for elderly patients who are clinically selected for revascularization (approximately 1 of 5 patients), so age alone should not disqualify a patient from early revascularization. (See Section VII.F.5 and also Section 7.6.5 of the full-text guidelines.)

**Percutaneous Coronary Intervention After Fibrinolysis****Class I**

1. In patients whose anatomy is suitable, PCI should be performed when there is objective evidence of recurrent MI. (*Level of Evidence: C*)
2. In patients whose anatomy is suitable, PCI should be performed for moderate or severe spontaneous or provable myocardial ischemia during recovery from STEMI. (*Level of Evidence: B*)
3. In patients whose anatomy is suitable, PCI should be performed for cardiogenic shock or hemodynamic instability. (See section on PCI for Cardiogenic Shock in Section VI.C.1.f.) (*Level of Evidence: B*)

**Class IIa**

1. It is reasonable to perform routine PCI in patients with LV ejection fraction (LVEF) less than or equal to 0.40, CHF, or serious ventricular arrhythmias. (*Level of Evidence: C*)
2. It is reasonable to perform PCI when there is documented clinical heart failure during the acute episode, even though subsequent evaluation shows preserved LV function (LVEF greater than 0.40). (*Level of Evidence: C*)

**Class IIb**

1. Routine PCI might be considered as part of an invasive strategy after fibrinolytic therapy. (*Level of Evidence: B*)

*Immediately After Successful Fibrinolysis.* Randomized prospective trials examined the efficacy and safety of immediate PCI after fibrinolysis.<sup>105,106,112</sup> These trials showed no benefit of routine PCI of the stenotic infarct artery immediately after fibrinolytic therapy. The strategy did not appear to salvage myocardium, improve LVEF, or prevent reinfarction or death. Those subjected to this approach appeared to have an increased incidence of adverse events, including bleeding, recurrent ischemia, emergency CABG, and death. These studies have not been repeated in the modern interventional era with improved equipment, improved antiplatelet and anticoagulant strategies, and coronary stents, thus leaving the question of routine PCI early after successful fibrinolysis

unresolved in contemporary practice. Studies of facilitated PCI are enrolling patients.<sup>113-116</sup>

**Hours to Days After Successful Fibrinolysis.** Great improvements in equipment, operator experience, and adjunctive pharmacotherapy have increased PCI success rates and decreased complications. More recently, the invasive strategy for NSTEMI patients has been given a Class I recommendation by the ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non-STEMI.<sup>117</sup> STEMI patients are increasingly being treated similarly as an extension of this approach. Although 6 published reports<sup>115,118-121,123</sup> and 1 preliminary report<sup>122</sup> support this strategy, randomized studies similar to those in NSTEMI need to be performed.

#### ACUTE SURGICAL REPERFUSION

##### **Class I**

**1. Emergency or urgent CABG in patients with STEMI should be undertaken in the following circumstances:**

- a. Failed PCI with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery. (*Level of Evidence: B*)
- b. Persistent or recurrent ischemia refractory to medical therapy in patients who have coronary anatomy suitable for surgery, have a significant area of myocardium at risk, and are not candidates for PCI or fibrinolytic therapy. (*Level of Evidence: B*)
- c. At the time of surgical repair of postinfarction ventricular septal rupture (VSR) or mitral valve insufficiency. (*Level of Evidence: B*)
- d. Cardiogenic shock in patients less than 75 years old with ST elevation, LBBB, or posterior MI who develop shock within 36 hours of STEMI, have severe multivessel or left main disease, and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: A*)
- e. Life-threatening ventricular arrhythmias in the presence of greater than or equal to 50% left main stenosis and/or triple-vessel disease. (*Level of Evidence: B*)

##### **Class IIa**

- 1. Emergency CABG can be useful as the primary reperfusion strategy in patients who have suitable anatomy, who are not candidates for fibrinolysis or PCI, and who are in the early hours (6 to 12 hours) of an evolving STEMI, especially if severe multivessel or left main disease is present. (*Level of Evidence: B*)
- 2. Emergency CABG can be effective in selected patients 75 years or older with ST elevation, LBBB, or posterior MI who develop shock within 36 hours of STEMI, have severe triple-vessel or left main disease, and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who are suitable for revascularization

and agree to invasive care may be selected for such an invasive strategy. (*Level of Evidence: B*)

#### **Class III**

- 1. Emergency CABG should not be performed in patients with persistent angina and a small area of risk if they are hemodynamically stable. (*Level of Evidence: C*)
- 2. Emergency CABG should not be performed in patients with successful epicardial reperfusion but unsuccessful microvascular reperfusion. (*Level of Evidence: C*)

#### PATIENTS WITH STEMI NOT RECEIVING REPERFUSION

Guideline-based recommendations for nonreperfusion treatments should not vary whether or not patients received reperfusion therapy. The major difference is that patients not receiving reperfusion therapy are considered to have a higher risk for future adverse events.<sup>124</sup>

#### ASSESSMENT OF REPERFUSION

##### **Class IIa**

- 1. It is reasonable to monitor the pattern of ST elevation, cardiac rhythm, and clinical symptoms over the 60 to 180 minutes after initiation of fibrinolytic therapy. Noninvasive findings suggestive of reperfusion include relief of symptoms, maintenance or restoration of hemodynamic and or electrical stability, and a reduction of at least 50% of the initial ST-segment elevation injury pattern on a follow-up ECG 60 to 90 minutes after initiation of therapy. (*Level of Evidence: B*)

Persistence of unrelenting ischemic chest pain, absence of resolution of the qualifying ST-segment elevation, and hemodynamic and/or electrical instability are generally indicators of failed pharmacological reperfusion and the need to consider rescue PCI. Aggressive medical support may be necessary in the interim. (See Rescue PCI in Section in VI.C.I.f.)

#### ANCILLARY THERAPY

##### Antithrombins as Ancillary Therapy to Reperfusion Therapy

##### *UNFRACTIONATED HEPARIN AS ANCILLARY THERAPY TO REPERFUSION THERAPY*

##### **Class I**

- 1. Patients undergoing percutaneous or surgical revascularization should be given UFH. (*Level of Evidence: C*)
- 2. UFH should be given intravenously to patients undergoing reperfusion therapy with alteplase, reteplase, or tenecteplase, with dosing as follows: bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per hour (maximum 1000 U/hr) adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds). (*Level of Evidence: C*)
- 3. UFH should be given intravenously to patients treated with nonselective fibrinolytic agents (streptokinase, anistreplase, or urokinase) who are at high risk for systemic emboli (large or anterior MI, atrial fibrilla-

- tion, previous embolus, or known LV thrombus). (*Level of Evidence: B*)
4. Platelet counts should be monitored daily in patients given UFH. (*Level of Evidence: C*)

#### *Class IIb*

1. It may be reasonable to administer UFH intravenously to patients undergoing reperfusion therapy with streptokinase. (*Level of Evidence: B*)

Because of the evidence that the measured effect of UFH on the aPTT is important for patient outcome and that the predominant variable mediating the effect of a given dose of heparin is weight,<sup>125</sup> it is important to administer the initial doses of UFH as a weight-adjusted bolus.<sup>126</sup> For fibrin-specific (alteplase, reteplase, and tenecteplase) fibrinolytic-treated patients, a 60 U/kg bolus followed by a maintenance infusion of 12 U/kg per hour (with a maximum of 4000 U bolus and 1000 U/h initial infusion for patients weighing greater than 70 kg) is recommended. The recommended weight-adjusted dose of UFH, when it is administered without fibrinolytics, is 60 to 70 U/kg IV bolus and 12 to 15 U/kg per hour infusion.<sup>117</sup>

#### *LOW-MOLECULAR-WEIGHT HEPARIN AS ANCILLARY THERAPY TO REPERFUSION THERAPY*

#### *Class IIb*

1. LMWH might be considered an acceptable alternative to UFH as ancillary therapy for patients less than 75 years of age who are receiving fibrinolytic therapy, provided that significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women) is not present. Enoxaparin (30 mg IV bolus followed by 1.0 mg/kg subcutaneous injection every 12 hours until hospital discharge) used in combination with full-dose tenecteplase is the most comprehensively studied regimen in patients less than 75 years of age. (*Level of Evidence: B*)

#### *Class III*

1. LMWH should not be used as an alternative to UFH as ancillary therapy in patients over 75 years of age who are receiving fibrinolytic therapy. (*Level of Evidence: B*)
2. LMWH should not be used as an alternative to UFH as ancillary therapy in patients less than 75 years of age who are receiving fibrinolytic therapy but have significant renal dysfunction (serum creatinine greater than 2.5 mg/dL in men or 2.0 mg/dL in women). (*Level of Evidence: B*)

The available data suggest that the rate of early (60 to 90 minutes) reperfusion of the infarct artery, either assessed angiographically or by noninvasive means, is not enhanced by administration of an LMWH. However, a generally consistent theme of a lower rate of reocclusion of the infarct artery, reinfarction, or recurrent ischemic events emerges in patients receiving LMWH regardless of whether the control group was given placebo or UFH.

#### *DIRECT ANTITHROMBINS AS ANCILLARY THERAPY TO REPERFUSION THERAPY*

#### *Class IIa*

1. In patients with known heparin-induced thrombocytopenia, it is reasonable to consider bivalirudin as a useful alternative to heparin to be used in conjunction with streptokinase. Dosing according to the HERO (Hirulog and Early Reperfusion or Occlusion)-2 regimen (a bolus of 0.25 mg/kg followed by an intravenous infusion of 0.5 mg/kg per hour for the first 12 hours and 0.25 mg/kg per hour for the subsequent 36 hours)<sup>127</sup> is recommended but with a reduction in the infusion rate if the PTT is above 75 seconds within the first 12 hours. (*Level of Evidence: B*)

On the basis of the data in the HERO-2 trial, the Writing Committee believed that bivalirudin could be considered an acceptable alternative to UFH in those STEMI patients who receive fibrinolysis with streptokinase, have heparin-induced thrombocytopenia, and who, in the opinion of the treating physician, would benefit from anticoagulation.

#### *Antiplatelets*

#### *ASPIRIN*

#### *Class I*

1. A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 to 162 mg) should be given indefinitely after STEMI to all patients without a true aspirin allergy. (*Level of Evidence: A*)

As discussed, aspirin should be given to the patient with suspected STEMI as early as possible and should be continued indefinitely, regardless of the strategy for reperfusion and regardless of whether additional antiplatelet agents are administered. True aspirin allergy is the only exception to this recommendation.

#### *THIENOPYRIDINES*

#### *Class I*

1. In patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and for up to 12 months in patients who are not at high risk for bleeding. (*Level of Evidence: B*)
2. In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days, and preferably for 7, unless the urgency for revascularization outweighs the risks of excess bleeding. (*Level of Evidence: B*)

#### *Class IIa*

1. Clopidogrel is probably indicated in patients receiving fibrinolytic therapy who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. (*Level of Evidence: C*)

Clopidogrel combined with aspirin is recommended for STEMI patients who undergo coronary stent implantation.<sup>128–132</sup> There are no safety data available regarding the combination of fibrinolytic agents and clopidogrel, but ongoing trials will provide this information in the future. However, in patients in whom aspirin is contraindicated because of aspirin sensitivity, clopidogrel is probably useful as a substitute for aspirin to reduce the risk of occlusion.<sup>133</sup> There are no safety data comparing 300 and 600 mg as loading doses for clopidogrel. We do not recommend routine administration of clopidogrel as pretreatment in patients who have not yet undergone diagnostic cardiac catheterization and in whom CABG surgery would be performed within 5 to 7 days if warranted.<sup>134</sup>

#### **GLYCOPROTEIN IIb/IIIa INHIBITORS**

##### **Class IIa**

- 1. It is reasonable to start treatment with abciximab as early as possible before primary PCI (with or without stenting) in patients with STEMI. (Level of Evidence: B)**

##### **Class IIb**

- 1. Treatment with tirofiban or eptifibatide may be considered before primary PCI (with or without stenting) in patients with STEMI. (Level of Evidence: C)**

The Writing Committee believes that it is reasonable to start treatment with abciximab as early as possible in patients undergoing primary PCI (with or without stenting) but, given the size and limitations of the available data set, assigned a Class IIa recommendation to this treatment. The data on tirofiban and eptifibatide in primary PCI are far more limited than for abciximab. However, given the common mode of action of the agents, a modest amount of angiographic data,<sup>135</sup> and general clinical experience to date, tirofiban or eptifibatide may be useful as antiplatelet therapy to support primary PCI for STEMI (with or without stenting) (Class IIb recommendation).

#### **OTHER PHARMACOLOGICAL MEASURES**

##### **Inhibition of Renin-Angiotensin-Aldosterone System**

##### **Class I**

- 1. An angiotensin converting enzyme (ACE) inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF less than 0.40, in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. (Level of Evidence: A)**
- 2. An angiotensin receptor blocker (ARB) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF less than 0.40. Valsartan and candesartan have established efficacy for this recommendation. (Level of Evidence: C)**

##### **Class IIa**

- 1. An ACE inhibitor administered orally within the first 24 hours of STEMI can be useful in patients without anterior infarction, pulmonary congestion, or LVEF less than 0.40 in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. The expected treatment benefit in such patients is less (5 lives saved per 1000 patients treated) than for patients with LV dysfunction. (Level of Evidence: B)**

##### **Class III**

- 1. An intravenous ACE inhibitor should not be given to patients within the first 24 hours of STEMI because of the risk of hypotension. (A possible exception may be patients with refractory hypertension.) (Level of Evidence: B)**

A number of large, randomized clinical trials have assessed the role of ACE inhibitors early in the course of acute MI. All trials with oral ACE inhibitors have shown benefit from their early use, including those in which early entry criteria included clinical suspicion of acute infarctions. Data from these trials indicate that ACE inhibitors should generally be started within the first 24 hours, ideally after fibrinolytic therapy has been completed and blood pressure has stabilized. ACE inhibitors should not be used if systolic blood pressure is less than 100 mm Hg or less than 30 mm Hg below baseline, if clinically relevant renal failure is present, if there is a history of bilateral stenosis of the renal arteries, or if there is known allergy to ACE inhibitors.

The use of ARBs has not been explored as thoroughly as ACE inhibitors in STEMI patients. However, clinical experience in the management of patients with heart failure and data from clinical trials in STEMI patients (see Sections 7.4.3 and 7.6.4 of the full-text guidelines) suggest that ARBs may be useful in patients with depressed LV function or clinical heart failure but who are intolerant of an ACE inhibitor. Use of aldosterone antagonists in STEMI patients is discussed in Sections 7.4.3 and 7.6.4 of the full-text guidelines.

##### **Metabolic Modulation of the Glucose-Insulin Axis**

#### ***STRICT GLUCOSE CONTROL DURING STEMI***

##### **Class I**

- 1. An insulin infusion to normalize blood glucose is recommended for patients with STEMI and complicated courses. (Level of Evidence: B)**

##### **Class IIa**

- 1. During the acute phase (first 24 to 48 hours) of the management of STEMI in patients with hyperglycemia, it is reasonable to administer an insulin infusion to normalize blood glucose, even in patients with an uncomplicated course. (Level of Evidence: B)**

- 2.** After the acute phase of STEMI, it is reasonable to individualize treatment of diabetics, selecting from a combination of insulin, insulin analogs, and oral hypoglycemic agents that achieve the best glycemic control and are well tolerated. (*Level of Evidence: C*)

Compelling evidence for tight glucose control in patients in the intensive care unit (a large proportion of whom were there after cardiac surgery) supports the importance of intensive insulin therapy to achieve a normal blood glucose level in critically ill patients.<sup>136,136a</sup>

#### Magnesium

##### *Class IIa*

- 1.** It is reasonable that documented magnesium deficits be corrected, especially in patients receiving diuretics before the onset of STEMI. (*Level of Evidence: C*)
- 2.** It is reasonable that episodes of torsade de pointes-type ventricular tachycardia (VT) associated with a prolonged QT interval be treated with 1 to 2 g of magnesium administered as an intravenous bolus over 5 minutes. (*Level of Evidence: C*)

##### *Class III*

- 1.** In the absence of documented electrolyte deficits or torsade de pointes-type VT, routine intravenous magnesium should not be administered to STEMI patients at any level of risk. (*Level of Evidence: A*)

#### Calcium Channel Blockers

##### *Class IIa*

- 1.** It is reasonable to give verapamil or diltiazem to patients in whom beta-blockers are ineffective or contraindicated (eg, bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with atrial fibrillation or flutter after STEMI in the absence of CHF, LV dysfunction, or atrioventricular (AV) block. (*Level of Evidence: C*)

##### *Class III*

- 1.** Diltiazem and verapamil are contraindicated in patients with STEMI and associated systolic LV dysfunction and CHF. (*Level of Evidence: A*)
- 2.** Nifedipine (immediate-release form) is contraindicated in treatment of STEMI because of the reflex sympathetic activation, tachycardia, and hypotension associated with its use. (*Level of Evidence: B*)

See the full-text guidelines for further explanation.

## VII. Hospital Management

### A. Location

#### *1. Coronary Care Unit*

##### *Class I*

- 1.** STEMI patients should be admitted to a quiet and comfortable environment that provides for continuous monitoring of the ECG and pulse oximetry and has

ready access to facilities for hemodynamic monitoring and defibrillation. (*Level of Evidence: C*)

- 2.** The patient's medication regimen should be reviewed to confirm the administration of aspirin and beta-blockers in an adequate dose to control heart rate and to assess the need for intravenous nitroglycerin for control of angina, hypertension, or heart failure. (*Level of Evidence: A*)
- 3.** The ongoing need for supplemental oxygen should be assessed by monitoring arterial oxygen saturation. When stable for 6 hours, the patient should be reassessed for oxygen need (ie, O<sub>2</sub> saturation of less than 90%), and discontinuation of supplemental oxygen should be considered. (*Level of Evidence: C*)
- 4.** Nursing care should be provided by individuals certified in critical care, with staffing based on the specific needs of patients and provider competencies, as well as organizational priorities. (*Level of Evidence: C*)
- 5.** Care of STEMI patients in the critical care unit (CCU) should be structured around protocols derived from practice guidelines. (*Level of Evidence: C*)
- 6.** Electrocardiographic monitoring leads should be based on the location and rhythm to optimize detection of ST deviation, axis shift, conduction defects, and dysrhythmias. (*Level of Evidence: B*)

##### *Class III*

- 1.** It is not an effective use of the CCU environment to admit terminally ill, "do not resuscitate" patients with STEMI, because clinical and comfort needs can be provided outside of a critical care environment. (*Level of Evidence: C*)

#### *2. Stepdown Unit*

##### *Class I*

- 1.** It is a useful triage strategy to admit low-risk STEMI patients who have undergone successful PCI directly to the stepdown unit for post-PCI care rather than to the CCU. (*Level of Evidence: C*)
- 2.** STEMI patients originally admitted to the CCU who demonstrate 12 to 24 hours of clinical stability (absence of recurrent ischemia, heart failure, or hemodynamically compromising dysrhythmias) should be transferred to the stepdown unit. (*Level of Evidence: C*)

##### *Class IIa*

- 1.** It is reasonable for patients recovering from STEMI who have clinically symptomatic heart failure to be managed on the stepdown unit, provided that facilities for continuous monitoring of pulse oximetry and appropriately skilled nurses are available. (*Level of Evidence: C*)
- 2.** It is reasonable for patients recovering from STEMI who have arrhythmias that are hemodynamically well-tolerated (eg, atrial fibrillation with a controlled ventricular response; paroxysms of nonsustained VT lasting less than 30 seconds) to be managed on the stepdown unit, provided that facilities for continuous monitoring of the ECG, defibrillators, and appropriately skilled nurses are available. (*Level of Evidence: C*)

***Class IIb***

1. Patients recovering from STEMI who have clinically significant pulmonary disease requiring high-flow supplemental oxygen or noninvasive mask ventilation/bilevel positive airway pressure (BIPAP)/continuous positive airway pressure (CPAP) may be considered for care on a stepdown unit provided that facilities for continuous monitoring of pulse oximetry and appropriately skilled nurses with a sufficient nurse:patient ratio are available. (*Level of Evidence: C*)

**B. Early, General Measures***1. Level of Activity****Class IIa***

1. After 12 to 24 hours, it is reasonable to allow patients with hemodynamic instability or continued ischemia to have bedside commode privileges. (*Level of Evidence: C*)

***Class III***

1. Patients with STEMI who are free of recurrent ischemic discomfort, symptoms of heart failure, or serious disturbances of heart rhythm should not be on bed rest for more than 12 to 24 hours. (*Level of Evidence: C*)

*2. Diet****Class I***

1. Patients with STEMI should be prescribed the NCEP Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes (TLC) diet, which focuses on reduced intake of fats and cholesterol, less than 7% of total calories as saturated fats, less than 200 mg of cholesterol per day, increased consumption of omega-3 fatty acids, and appropriate caloric intake for energy needs. (*Level of Evidence: C*)
2. Diabetic patients with STEMI should have an appropriate food group balance and caloric intake. (*Level of Evidence: B*)
3. Sodium intake should be restricted in STEMI patients with hypertension or heart failure. (*Level of Evidence: B*)

STEMI patients should receive a reduced saturated fat and cholesterol diet per the ATP III TLC approach.<sup>137</sup> (See VII.L.2 and Section 7.12.2 of the full-text guidelines.)

*3. Patient Education in the Hospital Setting****Class I***

1. Patient counseling to maximize adherence to evidence-based post-STEMI treatments (eg, compliance with taking medication, exercise prescription, and smoking cessation) should begin during the early phase of hospitalization, occur intensively at discharge, and continue at follow-up visits with providers and through cardiac rehabilitation programs and community support groups, as appropriate. (*Level of Evidence: C*)
2. Critical pathways and protocols and other quality-improvement tools (eg, the ACC "Guidelines Applied in Practice" and the AHA's "Get with the Guidelines") should be used to improve the application of evidence-

based treatments by patients with STEMI, caregivers, and institutions. (*Level of Evidence: C*)

Patient education should be viewed as a continuous process that should be part of every patient encounter (ie, on hospital arrival, inpatient admission, discharge, and at follow-up visits).

**4. Analgesia/Anxiolytics*****Class IIa***

1. It is reasonable to use anxiolytic medications in STEMI patients to alleviate short-term anxiety or altered behavior related to hospitalization for STEMI. (*Level of Evidence: C*)
2. It is reasonable to routinely assess the patient's anxiety level and manage it with behavioral interventions and referral for counseling. (*Level of Evidence: C*)

Anxiety and depression are prevalent in patients hospitalized for STEMI because patients are confronted with a diagnosis that is major, both psychologically and physically.<sup>138,139</sup> Anxiety has been demonstrated to predict in-hospital recurrent ischemia and arrhythmias<sup>140</sup> and cardiac events during the first year after an MI.<sup>141</sup>

**C. Risk Stratification During Early Hospital Course**

Risk stratification is a continuous process and requires the updating of initial assessments with data obtained during the hospital stay. Indicators of failed reperfusion (eg, recurrence of chest pain and persistence of ECG findings indicating infarction) identify a patient who should undergo coronary angiography. Similarly, findings consistent with mechanical complications (eg, sudden onset of heart failure or presence of a new murmur) herald increased risk and suggest the need for rapid intervention. For patients who did not undergo primary reperfusion, changes in clinical status (eg, development of shock) may herald a worsening clinical status and are an indication for coronary angiography. Patients with a low risk of complications may be candidates for early discharge. The lowest-risk patients are those who did not have STEMI despite the initial suspicions. Clinicians should strive to identify such patients within 8 to 12 hours of onset of symptoms. Serial sampling of serum cardiac biomarkers and use of 12-lead ECGs and their interpretation in the context of the number of hours that have elapsed since onset of the patient's symptoms can determine the presence of STEMI better than adherence to a rigid protocol that requires that a specified number of samples be drawn in the hospital.

**D. Medication Assessment***1. Beta-Blockers****Class I***

1. Patients receiving beta-blockers within the first 24 hours of STEMI without adverse effects should continue to receive them during the early convalescent phase of STEMI. (*Level of Evidence: A*)

2. Patients without contraindications to beta-blockers who did not receive them within the first 24 hours after STEMI should have them started in the early convalescent phase. (*Level of Evidence: A*)
3. Patients with early contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for beta-blocker therapy. (*Level of Evidence: C*)

There is overwhelming evidence for the benefits of early beta-blockade in patients with STEMI and without contraindications to their use (see Section 6.3.1.5 of the full-text guidelines). Benefits have been demonstrated for patients with and without concomitant fibrinolytic therapy, both early and late after STEMI. Meta-analysis of trials from the prefibrinolytic era involving more than 24 000 patients receiving beta-blockers have shown a 14% relative risk reduction in mortality through 7 days and a 23% reduction in long-term mortality.<sup>142</sup>

## *2. Nitroglycerin*

### *Class I*

1. Intravenous nitroglycerin is indicated in the first 48 hours after STEMI for treatment of persistent ischemia, CHF, or hypertension. The decision to administer intravenous nitroglycerin and the dose used should not preclude therapy with other proven mortality-reducing interventions, such as beta-blockers or ACE inhibitors. (*Level of Evidence: B*)
2. Intravenous, oral, or topical nitrates are useful beyond the first 48 hours after STEMI for treatment of recurrent angina or persistent CHF if their use does not preclude therapy with beta-blockers or ACE inhibitors. (*Level of Evidence: B*)

### *Class IIb*

1. The continued use of nitrate therapy beyond the first 24 to 48 hours in the absence of continued or recurrent angina or CHF may be helpful, although the benefit is likely to be small and is not well established in contemporary practice. (*Level of Evidence: B*)

### *Class III*

1. Nitrates should not be administered to patients with systolic pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 bpm), tachycardia (more than 100 bpm) or RV infarction. (*Level of Evidence: C*)

## *3. Inhibition of the Renin-Angiotensin-Aldosterone System*

### *Class I*

1. An ACE inhibitor should be administered orally during convalescence from STEMI in patients who tolerate this class of medication, and it should be continued over the long term. (*Level of Evidence: A*)
2. An ARB should be administered to STEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of heart failure or LVEF less than 0.40. Valsartan and candesartan have dem-

onstrated efficacy for this recommendation. (*Level of Evidence: B*)

3. Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either symptomatic heart failure or diabetes. (*Level of Evidence: A*)

### *Class IIa*

1. In STEMI patients who tolerate ACE inhibitors, an ARB can be useful as an alternative to ACE inhibitors provided there are either clinical or radiological signs of heart failure or LVEF is less than 0.40. Valsartan and candesartan have established efficacy for this recommendation. (*Level of Evidence: B*)

The use of ACE inhibitors in the initial management of the STEMI patient was reviewed previously. The proportional benefit of ACE inhibitor therapy is largest in higher-risk subgroups, including those with previous infarction, heart failure, depressed LVEF, and tachycardia.<sup>143-145</sup> Survival benefit for patients more than 75 years old and for a low-risk subgroup without the features noted above is equivocal.<sup>144,145</sup>

Aldosterone blockade is another means of inhibiting the renin-angiotensin-aldosterone system that has been applied to patients in the post-STEMI setting. RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) support the long-term use of an aldosterone blocker in STEMI patients with heart failure, an ejection fraction of 0.40 or less, or both, provided the serum creatinine is less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women and serum potassium concentration is less than or equal to 5.0 mEq/L.<sup>146,147</sup>

The use of ARBs after STEMI has not been explored as thoroughly as ACE inhibitors in STEMI patients.<sup>148,149</sup> Given the extensive randomized trial and routine clinical experience with ACE inhibitors, they remain the logical first agent for inhibition of the renin-angiotensin-aldosterone system in patients convalescing from STEMI.<sup>150</sup> Valsartan monotherapy (target dose 160 mg twice daily) should be administered to STEMI patients who are intolerant of ACE inhibitors and have evidence of LV dysfunction. Valsartan monotherapy can be a useful alternative to ACE inhibitors; the decision in individual patients may be influenced by physician and patient preference, cost, and anticipated side-effect profile.

### *4. Antiplatelets*

### *Class I*

1. Aspirin 162 to 325 mg should be given on day 1 of STEMI and in the absence of contraindications should be continued indefinitely on a daily basis thereafter at a dose of 75 to 162 mg. (*Level of Evidence: A*)
2. A thienopyridine (preferably clopidogrel) should be administered to patients who are unable to take aspirin

- because of hypersensitivity or major gastrointestinal intolerance. (*Level of Evidence: C*)
3. For patients taking clopidogrel for whom CABG is planned, if possible, the drug should be withheld for at least 5 days, and preferably for 7, unless the urgency for revascularization outweighs the risks of bleeding. (*Level of Evidence: B*)
  4. For patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation and for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel) and up to 12 months in patients who are not at high risk for bleeding. (*Level of Evidence: B*)

#### **5. Antithrombotics**

##### ***Class I***

1. Intravenous UFH (bolus of 60 U/kg, maximum 4000 U IV; initial infusion 12 U/kg per hour, maximum of 1000 U/h) or LMWH should be used in patients after STEMI who are at high risk for systemic emboli (large or anterior MI, atrial fibrillation, previous embolus, known LV thrombus, or cardiogenic shock). (*Level of Evidence: C*)

##### ***Class IIa***

1. It is reasonable that STEMI patients not undergoing reperfusion therapy who do not have a contraindication to anticoagulation be treated with intravenous or subcutaneous UFH or with subcutaneous LMWH for at least 48 hours. In patients whose clinical condition necessitates prolonged bedrest and/or minimized activities, it is reasonable that treatment be continued until the patient is ambulatory. (*Level of Evidence: C*)

##### ***Class IIb***

1. Prophylaxis for deep venous thrombosis (DVT) with subcutaneous LMWH (dosed appropriately for specific agent) or with subcutaneous UFH, 7500 U to 12 500 U twice per day until completely ambulatory, may be useful, but the effectiveness of such a strategy is not well established in the contemporary era of routine aspirin use and early mobilization. (*Level of Evidence: C*)

#### **6. Oxygen**

##### ***Class I***

1. Supplemental oxygen therapy should be continued beyond the first 6 hours in STEMI patients with arterial oxygen desaturation ( $\text{SaO}_2$  less than 90%) or overt pulmonary congestion. (*Level of Evidence: C*)

#### **E. Estimation of Infarct Size**

Measurement of infarct size is an important element in the overall care of patients with STEMI. There are 5 major modalities that can be applied to sizing MI.

##### ***1. Electrocardiographic Techniques***

##### ***Class I***

1. All patients with STEMI should have follow-up ECGs at 24 hours and at hospital discharge to assess the

success of reperfusion and/or the extent of infarction, defined in part by the presence or absence of new Q waves. (*Level of Evidence: B*)

#### **2. Cardiac Biomarker Methods**

The most widely accepted method for quantifying infarction has been the use of serial creatine kinase and the creatine kinase-MB isoenzyme.

#### ***3. Radionuclide Imaging***

The most comprehensive assessment of STEMI with radionuclide imaging was developed with the technetium sestamibi SPECT approach.<sup>151</sup> This approach is well delineated in the ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging.<sup>152</sup>

#### ***4. Echocardiography***

Global and regional LV function provides an assessment of the functional consequences of STEMI and ischemia. Readers are referred to the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography<sup>153</sup> and to Section 7.11.1.2 of the full-text STEMI guidelines.

#### ***5. Magnetic Resonance Imaging***

Measurement of infarct size by MRI is a promising new technique that affords enhanced spatial resolution, thereby permitting more accurate assessment of both the transmural and circumferential extent of infarction.<sup>154</sup> However, additional experience and comparison with other methods of assessing infarct size are required before any clinical recommendations can be provided.

#### **F. Hemodynamic Disturbances**

##### ***1. Hemodynamic Assessment***

##### ***Class I***

1. Pulmonary artery catheter monitoring should be performed for the following:

- a. Progressive hypotension, when unresponsive to fluid administration or when fluid administration may be contraindicated. (*Level of Evidence: C*)
- b. Suspected mechanical complications of STEMI, (ie, VSR, papillary muscle rupture, or free wall rupture with pericardial tamponade) if an echocardiogram has not been performed. (*Level of Evidence: C*)

2. Intra-arterial pressure monitoring should be performed for the following:

- a. Patients with severe hypotension (systolic arterial pressure less than 80 mm Hg). (*Level of Evidence: C*)
- b. Patients receiving vasopressor/inotropic agents. (*Level of Evidence: C*)
- c. Cardiogenic shock. (*Level of Evidence: C*)

##### ***Class IIa***

1. Pulmonary artery catheter monitoring can be useful for the following:

- a. Hypotension in a patient without pulmonary congestion who has not responded to an initial trial of fluid administration. (*Level of Evidence: C*)
  - b. Cardiogenic shock. (*Level of Evidence: C*)
  - c. Severe or progressive CHF or pulmonary edema that does not respond rapidly to therapy. (*Level of Evidence: C*)
  - d. Persistent signs of hypoperfusion without hypotension or pulmonary congestion. (*Level of Evidence: C*)
  - e. Patients receiving vasopressor/inotropic agents. (*Level of Evidence: C*)
2. Intra-arterial pressure monitoring can be useful for patients receiving intravenous sodium nitroprusside or other potent vasodilators. (*Level of Evidence: C*)

#### **Class IIb**

1. Intra-arterial pressure monitoring might be considered in patients receiving intravenous inotropic agents. (*Level of Evidence: C*)

#### **Class III**

1. Pulmonary artery catheter monitoring is not recommended in patients with STEMI without evidence of hemodynamic instability or respiratory compromise. (*Level of Evidence: C*)
2. Intra-arterial pressure monitoring is not recommended for patients with STEMI who have no pulmonary congestion and have adequate tissue perfusion without use of circulatory support measures. (*Level of Evidence: C*)

#### **2. Hypotension**

##### **Class I**

1. Rapid volume loading with an IV infusion should be administered to patients without clinical evidence for volume overload. (*Level of Evidence: C*)
2. Rhythm disturbances or conduction abnormalities causing hypotension should be corrected. (*Level of Evidence: C*)
3. Intra-aortic balloon counterpulsation should be performed in patients who do not respond to other interventions, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: B*)
4. Vasopressor support should be given for hypotension that does not resolve after volume loading. (*Level of Evidence: C*)
5. Echocardiography should be used to evaluate mechanical complications unless these are assessed by invasive measures. (*Level of Evidence: C*)

#### **3. Low-Output State**

##### **Class I**

1. LV function and potential presence of a mechanical complication should be assessed by echocardiography if these have not been evaluated by invasive measures. (*Level of Evidence: C*)
2. Recommended treatments for low-output states include:
  - a. Inotropic support. (*Level of Evidence: B*)

- b. Intra-aortic counterpulsation. (*Level of Evidence: B*)
- c. Mechanical reperfusion with PCI or CABG. (*Level of Evidence: B*)
- d. Surgical correction of mechanical complications. (*Level of Evidence: B*)

#### **Class III**

1. Beta-blockers or calcium channel antagonists should not be administered to patients in a low-output state due to pump failure. (*Level of Evidence: B*)

A preshock state of hypoperfusion with normal blood pressure may develop before circulatory collapse and is manifested by cold extremities, cyanosis, oliguria, or decreased mentation.<sup>155</sup> Hospital mortality is high, so these patients should be aggressively diagnosed and treated as though they had cardiogenic shock. The initial pharmacological intervention for low cardiac output is often a dobutamine infusion. Intra-aortic counterpulsation therapy may be required to improve coronary artery perfusion pressure if hypotension is present. If the blood pressure permits, afterload-reducing agents should be added to decrease cardiac work and pulmonary congestion. Coronary artery revascularization of ischemic myocardium with either PCI or CABG has been shown to decrease mortality in patients with cardiogenic shock and is strongly recommended in suitable candidates.<sup>75,108</sup> Likewise, patients with VSR, papillary muscle rupture, or free wall rupture with pericardial tamponade may benefit from emergency surgical repair.

#### **4. Pulmonary Congestion**

##### **Class I**

1. Oxygen supplementation to arterial saturation greater than 90% is recommended for patients with pulmonary congestion. (*Level of Evidence: C*)
2. Morphine sulfate should be given to patients with pulmonary congestion. (*Level of Evidence: C*)
3. ACE inhibitors, beginning with titration of a short-acting ACE inhibitor with a low initial dose (eg, 1 to 6.25 mg of captopril) should be given to patients with pulmonary edema unless the systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline. Patients with pulmonary congestion and marginal or low blood pressure often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion. (*Level of Evidence: A*)
4. Nitrates should be administered to patients with pulmonary congestion unless the systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline. Patients with pulmonary congestion and marginal or low blood pressure often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion. (*Level of Evidence: C*)
5. A diuretic (low- to intermediate-dose furosemide, or torsemide or bumetanide) should be administered to patients with pulmonary congestion if there is associ-

- ated volume overload. Caution is advised for patients who have not received volume expansion. (*Level of Evidence: C*)
6. Beta-blockade should be initiated before discharge for secondary prevention. For those who remain in heart failure throughout the hospitalization, low doses should be initiated, with gradual titration on an outpatient basis. (*Level of Evidence: B*)
  7. Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either symptomatic heart failure or diabetes. (*Level of Evidence: A*)
  8. Echocardiography should be performed urgently to estimate LV and RV function and to exclude a mechanical complication. (*Level of Evidence: C*)

#### *Class IIb*

1. It may be reasonable to insert an intra-aortic balloon pump (IABP) for the management of patients with refractory pulmonary congestion. (*Level of Evidence: C*)

#### *Class III*

1. Beta-blockers or calcium channel blockers should not be administered acutely to STEMI patients with frank cardiac failure evidenced by pulmonary congestion or signs of a low-output state. (*Level of Evidence: B*)

The immediate management goals include adequate oxygenation and preload reduction to relieve pulmonary congestion. Because of sympathetic stimulation, the blood pressure should be elevated in the presence of pulmonary edema. Patients with this appropriate response can typically tolerate the required medications, all of which lower blood pressure. However, iatrogenic cardiogenic shock may result from aggressive simultaneous use of agents that cause hypotension, initiating a cycle of hypoperfusion-ischemia. If acute pulmonary edema is not associated with elevation of the systemic blood pressure, impending cardiogenic shock must be suspected. If pulmonary edema is associated with hypotension, cardiogenic shock is diagnosed. Those patients often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion (Figure 4) (See Section VII.F.5, and see Section 7.6.5 of the full-text guidelines).

#### *5. Cardiogenic Shock*

##### *Class I*

1. Intra-aortic balloon counterpulsation is recommended for STEMI patients when cardiogenic shock is not quickly reversed with pharmacological therapy. The IABP is a stabilizing measure for angiography and prompt revascularization. (*Level of Evidence: B*)
2. Intra-arterial monitoring is recommended for the management of STEMI patients with cardiogenic shock. (*Level of Evidence: C*)

3. Early revascularization, either PCI or CABG, is recommended for patients less than 75 years old with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: A*)
4. Fibrinolytic therapy should be administered to STEMI patients with cardiogenic shock who are unsuitable for further invasive care and do not have contraindications to fibrinolysis. (*Level of Evidence: B*)
5. Echocardiography should be used to evaluate mechanical complications unless these are assessed by invasive measures. (*Level of Evidence: C*)

#### *Class IIa*

1. Pulmonary artery catheter monitoring can be useful for the management of STEMI patients with cardiogenic shock. (*Level of Evidence: C*)
2. Early revascularization, either PCI or CABG, is reasonable for selected patients 75 years or older with ST elevation or LBBB who develop shock within 36 hours of MI and are suitable for revascularization that can be performed within 18 hours of shock. Patients with good prior functional status who agree to invasive care may be selected for such an invasive strategy. (*Level of Evidence: B*)

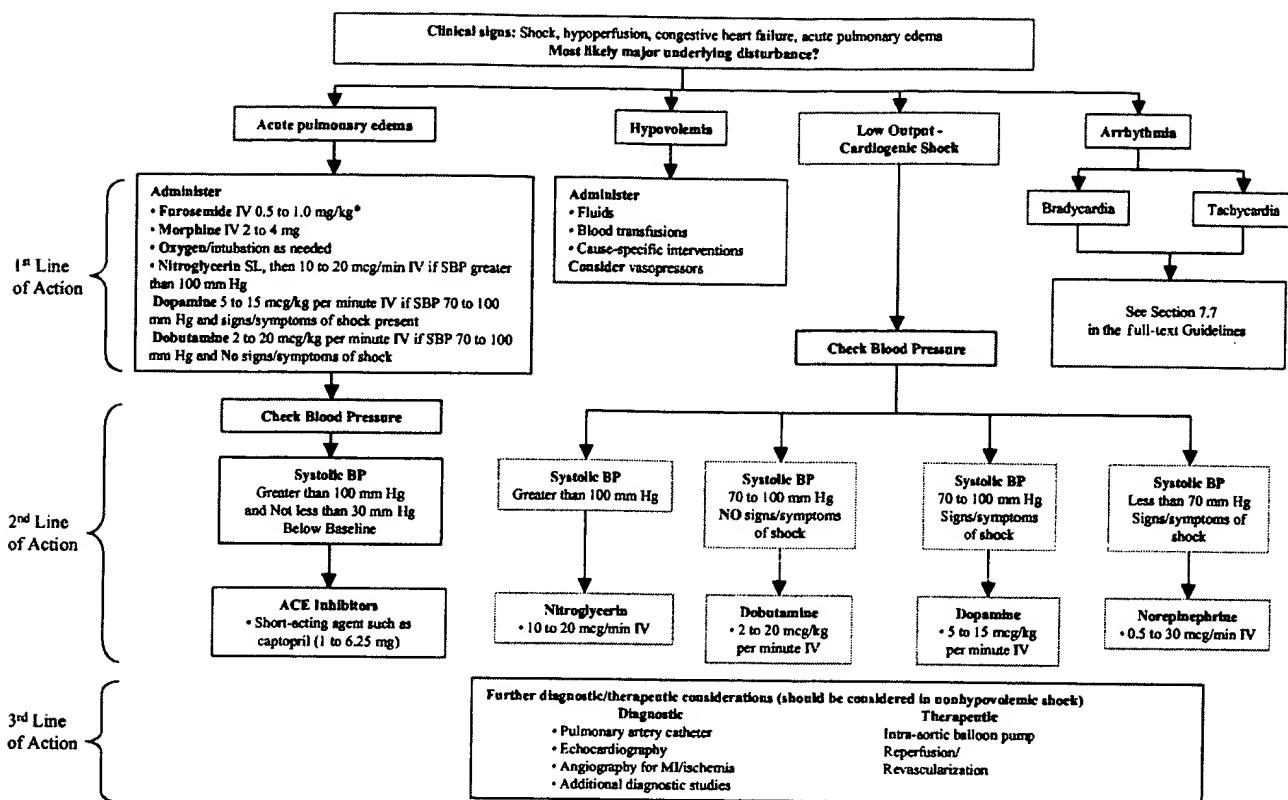
Given the large overall treatment benefit of 13 lives saved per 100 patients treated in the SHOCK trial, early revascularization is recommended for those less than 75 years who are suitable for revascularization.<sup>75,108,156</sup> Two other large registries reported a substantial survival benefit for elderly patients who were selected clinically on the basis of physician judgment.

Interventions should be performed as soon as possible. It is recommended that patients who arrive at the hospital in cardiogenic shock (15% of cases) or who develop it after hospital arrival (85%) should be transferred to a regional tertiary care center with revascularization facilities experienced with these patients. When shock has resolved, ACE inhibitors and beta-blockers, initiated in low doses with progressive increases as recommended in the CHF guidelines, should be administered before discharge.<sup>157</sup> (See Section 7.6.7.6 of the full-text guidelines for discussion of mechanical support for the failing heart.)

#### *6. Right Ventricular Infarction*

##### *Class I*

1. Patients with inferior STEMI and hemodynamic compromise should be assessed with a right precordial V<sub>4R</sub> lead to detect ST-segment elevation and an echocardiogram to screen for RV infarction. (See the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography.) (*Level of Evidence: B*)
2. The following principles apply to therapy of patients with STEMI and RV infarction and ischemic dysfunction:
  - a. Early reperfusion should be achieved if possible. (*Level of Evidence: C*)



**Figure 4.** Emergency management of complicated ST-elevation myocardial infarction. The emergency management of patients with cardiogenic shock, acute pulmonary edema, or both is outlined. SBP indicates systolic blood pressure; IV, intravenous; BP, blood pressure; ACE, angiotensin converting enzyme; MI, myocardial infarction. \*Furosemide less than 0.5 mg/kg for new-onset acute pulmonary edema without hypovolemia; 1 mg/kg for acute or chronic volume overload, renal insufficiency. Nesiritide has not been studied adequately in patients with STEMI. Combinations of medications, eg, dobutamine and dopamine, may be used. Modified with permission from Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: Part 7: The Era of Reperfusion. Section 1: Acute Coronary Syndromes (Acute Myocardial Infarction). *Circulation*. 2000;102(suppl 1):I-172-I-216.<sup>26</sup>

- AV synchrony should be achieved, and bradycardia should be corrected. (*Level of Evidence: C*)
- RV preload should be optimized, which usually requires initial volume challenge in patients with hemodynamic instability provided the jugular venous pressure is normal or low. (*Level of Evidence: C*)
- RV afterload should be optimized, which usually requires therapy for concomitant LV dysfunction. (*Level of Evidence: C*)
- Inotropic support should be used for hemodynamic instability not responsive to volume challenge. (*Level of Evidence: C*)

#### Class IIa

- After infarction that leads to clinically significant RV dysfunction, it is reasonable to delay CABG surgery for 4 weeks to allow recovery of contractile performance. (*Level of Evidence: C*)

Treatment of RV ischemia/infarction includes early maintenance of RV preload, reduction of RV afterload, inotropic support of the dysfunctional RV, early reperfusion,<sup>158</sup> and maintenance of AV synchrony.

#### 7. Mechanical Causes of Heart Failure/Low-Output Syndrome

##### a. Diagnosis

On physical examination, the presence of a new cardiac murmur indicates the possibility of either a VSR or MR. A precise diagnosis can usually be established with transthoracic or transesophageal echocardiography.

##### b. Mitral Valve Regurgitation

##### Class I

- Patients with acute papillary muscle rupture should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (*Level of Evidence: B*)
- CABG surgery should be undertaken at the same time as mitral valve surgery. (*Level of Evidence: B*)

The patient should be stabilized with an IABP, inotropic support, and afterload reduction (to reduce regurgitant volume and pulmonary congestion) while emergency surgery is arranged.

*c. Ventricular Septal Rupture After STEMI****Class I***

- 1. Patients with STEMI complicated by the development of a VSR should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (Level of Evidence: B)**
- 2. CABG should be undertaken at the same time as repair of the VSR. (Level of Evidence: B)**

Insertion of an IABP and prompt surgical referral are recommended for almost every patient with an acute VSR. Invasive monitoring is recommended in all patients, together with judicious use of inotropes and a vasodilator to maintain optimal hemodynamics. Surgical repair usually involves excision of all necrotic tissue and patch repair of the VSR, together with coronary artery grafting.

*d. Left Ventricular Free-Wall Rupture****Class I***

- 1. Patients with free-wall rupture should be considered for urgent cardiac surgical repair, unless further support is considered futile because of the patient's wishes or contraindications/unsuitability for further invasive care. (Level of Evidence: B)**
- 2. CABG should be undertaken at the same time as repair of free-wall rupture. (Level of Evidence: C)**

Surgery includes repair of the ventricle by a direct suture technique or patch to cover the ventricular perforation<sup>159</sup> in addition to CABG as needed.

*e. Left Ventricular Aneurysm****Class IIa***

- 1. It is reasonable that patients with STEMI who develop a ventricular aneurysm associated with intractable ventricular tachyarrhythmias and/or pump failure unresponsive to medical and catheter-based therapy be considered for LV aneurysmectomy and CABG surgery. (Level of Evidence: B)**

*f. Mechanical Support of the Failing Heart***INTRAOCTIC BALLOON COUNTERPULSATION*****Class I***

- 1. Intra-aortic balloon counterpulsation should be used in STEMI patients with hypotension (systolic blood pressure less than 90 mm Hg or 30 mm Hg below baseline mean arterial pressure) who do not respond to other interventions, unless further support is futile because of the patient's wishes or contraindications/unsuitability for further invasive care. See Section 7.6.2 of the full-text guidelines. (Level of Evidence: B)**
- 2. Intra-aortic balloon counterpulsation is recommended for STEMI patients with low-output state. See Section 7.6.3 of the full-text guidelines. (Level of Evidence: B)**
- 3. Intra-aortic balloon counterpulsation is recommended for STEMI patients when cardiogenic shock is not**

quickly reversed with pharmacological therapy. IABP is a stabilizing measure for angiography and prompt revascularization. See Section 7.6.5 of the full-text guidelines. (*Level of Evidence: B*)

- 4. Intra-aortic balloon counterpulsation should be used in addition to medical therapy for STEMI patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor LV function, or a large area of myocardium at risk. Such patients should be referred urgently for cardiac catheterization and should undergo revascularization as needed. See Section 7.8.2 of the full-text guidelines. (Level of Evidence: C)**

***Class IIa***

- 1. It is reasonable to manage STEMI patients with refractory polymorphic VT with intra-aortic balloon counterpulsation to reduce myocardial ischemia. See Section 7.7.1.2 of the full-text guidelines. (Level of Evidence: B)**

***Class IIb***

- 1. It may be reasonable to use intra-aortic balloon counterpulsation in the management of STEMI patients with refractory pulmonary congestion. See Section 7.6.4 of the full-text guidelines. (Level of Evidence: C)**

Selected patients with cardiogenic shock after STEMI, especially if not candidates for revascularization, may be considered for either a short- or long-term mechanical support device to serve as a bridge to recovery or to subsequent cardiac transplantation.

**G. Arrhythmias After STEMI*****1. Ventricular Arrhythmias******a. Ventricular Fibrillation******Class I***

- 1. Ventricular fibrillation (VF) or pulseless VT should be treated with an unsynchronized electric shock with an initial monophasic shock energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and then, if necessary, a third shock of 360 J. (Level of Evidence: B)**

***Class IIa***

- 1. It is reasonable that VF or pulseless VT that is refractory to electrical shock be treated with amiodarone (300 mg or 5 mg/kg, IV bolus) followed by a repeat unsynchronized electric shock. (Level of Evidence: B)**
- 2. It is reasonable to correct electrolyte and acid-base disturbances (potassium greater than 4.0 mEq/L and magnesium greater than 2.0 mg/dL) to prevent recurrent episodes of VF once an initial episode of VF has been treated. (Level of Evidence: C)**

***Class IIb***

- 1. It may be reasonable to treat VT or shock-refractory VF with boluses of intravenous procainamide. How-**

ever, this has limited value owing to the length of time required for administration. (*Level of Evidence: C*)

### **Class III**

1. Prophylactic administration of antiarrhythmic therapy is not recommended when using fibrinolytic agents. (*Level of Evidence: B*)

There is no convincing evidence that the prophylactic use of lidocaine reduces mortality, and the prior practice of routine (prophylactic) administration of lidocaine to all patients with known or suspected STEMI has been largely abandoned. VF should be treated with an unsynchronized electric shock using an initial monophasic shock energy of 200 J. If this is unsuccessful, a second shock using 200 to 300 J and, if necessary, a third shock using 360 J are indicated.<sup>160</sup>

#### *b. Ventricular Tachycardia*

### **Class I**

1. Sustained (more than 30 seconds or causing hemodynamic collapse) polymorphic VT should be treated with an unsynchronized electric shock with an initial monophasic shock energy of 200 J; if unsuccessful, a second shock of 200 to 300 J should be given, and, if necessary, a third shock of 360 J. (*Level of Evidence: B*)
2. Episodes of sustained monomorphic VT associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with a synchronized electric shock of 100 J initial monophasic shock energy. Increasing energies may be used if not initially successful. Brief anesthesia is desirable if hemodynamically tolerable. (*Level of Evidence: B*)
3. Sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) should be treated with:
  - a. Amiodarone: 150 mg infused over 10 minutes (alternative dose 5 mg/kg); repeat 150 mg every 10 to 15 minutes as needed. Alternative infusion: 360 mg over 6 hours (1 mg/min), then 540 mg over the next 18 hours (0.5 mg/min). The total cumulative dose, including additional doses given during cardiac arrest, must not exceed 2.2 g over 24 hours. (*Level of Evidence: B*)
  - b. Synchronized electrical cardioversion starting at monophasic energies of 50 J (brief anesthesia is necessary). (*Level of Evidence: B*)

### **Class IIa**

1. It is reasonable to manage refractory polymorphic VT by:
  - a. Aggressive attempts to reduce myocardial ischemia and adrenergic stimulation, including therapies such as beta-adrenoceptor blockade, IABP use, and consideration of emergency PCI/CABG surgery. (*Level of Evidence: B*)

- b. Aggressive normalization of serum potassium to greater than 4.0 mEq/L and of magnesium to greater than 2.0 mg/dL. (*Level of Evidence: C*)
- c. If the patient has bradycardia to a rate less than 60 beats per minute or long QTc, temporary pacing at a higher rate may be instituted. (*Level of Evidence: C*)

### **Class IIb**

1. It is may be useful to treat sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension (blood pressure less than 90 mm Hg) with a procainamide bolus and infusion. (*Level of Evidence: C*)

### **Class III**

1. The routine use of prophylactic antiarrhythmic drugs (ie, lidocaine) is not indicated for suppression of isolated ventricular premature beats, couplets, runs of accelerated idioventricular rhythm, or nonsustained VT. (*Level of Evidence: B*)
2. The routine use of prophylactic antiarrhythmic therapy is not indicated when fibrinolytic agents are administered. (*Level of Evidence: B*)

*Management Strategies for VT.* Cardioversion is always indicated for episodes of sustained hemodynamically compromising VT.<sup>161</sup> Episodes of sustained VT that are somewhat better tolerated hemodynamically may initially be treated with drug regimens, including amiodarone or procainamide.

#### *c. Ventricular Premature Beats*

### **Class III**

1. Treatment of isolated ventricular premature beats, couplets, and nonsustained VT is not recommended unless they lead to hemodynamic compromise. (*Level of Evidence: A*)

Before the present era of care of the STEMI patient with antiplatelet therapy, beta-blockade, ACE inhibitors, and, above all, reperfusion strategies, it was thought that ventricular warning arrhythmias preceded VF. Careful monitoring has refuted this concept, and treatment of these rhythm disturbances is not recommended unless they lead to hemodynamic compromise.

#### *d. Accelerated Idioventricular Rhythms and Accelerated Junctional Rhythms*

### **Class III**

1. Antiarrhythmic therapy is not indicated for accelerated idioventricular rhythm. (*Level of Evidence: C*)
2. Antiarrhythmic therapy is not indicated for accelerated junctional rhythm. (*Level of Evidence: C*)

#### *e. Implantable Cardioverter Defibrillator Implantation in Patients After STEMI*

### **Class I**

1. An implantable cardioverter-defibrillator (ICD) is indicated for patients with VF or hemodynamically

significant sustained VT more than 2 days after STEMI, provided the arrhythmia is not judged to be due to transient or reversible ischemia or reinfarction. (*Level of Evidence: A*)

2. An ICD is indicated for patients without spontaneous VF or sustained VT more than 48 hours after STEMI whose STEMI occurred at least 1 month previously, who have an LVEF between 0.31 and 0.40, demonstrate additional evidence of electrical instability (eg, nonsustained VT), and have inducible VF or sustained VT on electrophysiological testing. (*Level of Evidence: B*)

#### *Class IIa*

1. If there is reduced LVEF (0.30 or less), at least 1 month after STEMI and 3 months after coronary artery revascularization, it is reasonable to implant an ICD in post STEMI patients without spontaneous VF or sustained VT more than 48 hours after STEMI. (*Level of Evidence: B*)

#### *Class IIb*

1. The usefulness of an ICD is not well established in STEMI patients without spontaneous VF or sustained VT more than 48 hours after STEMI who have a reduced LVEF (0.31 to 0.40) at least 1 month after STEMI but who have no additional evidence of electrical instability (eg, nonsustained VT). (*Level of Evidence: B*)
2. The usefulness of an ICD is not well established in STEMI patients without spontaneous VF or sustained VT more than 48 hours after STEMI who have a reduced LVEF (0.31 to 0.40) at least 1 month after STEMI and additional evidence of electrical instability (eg, nonsustained VT) but who do not have inducible VF or sustained VT on electrophysiological testing. (*Level of Evidence: B*)

#### *Class III*

1. An ICD is not indicated in STEMI patients who do not experience spontaneous VF or sustained VT more than 48 hours after STEMI and in whom the LVEF is greater than 0.40 at least 1 month after STEMI. (*Level of Evidence: C*)

See the full-text guidelines for discussion.

#### *2. Supraventricular Arrhythmias/Atrial Fibrillation*

##### *Class I*

1. Sustained atrial fibrillation and atrial flutter in patients with hemodynamic compromise or ongoing ischemia should be treated with one or more of the following:

- a. Synchronized cardioversion with an initial monophasic shock of 200 J for atrial fibrillation and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. (*Level of Evidence: C*)
- b. For episodes of atrial fibrillation that do not respond to electrical cardioversion or recur after

a brief period of sinus rhythm, the use of antiarrhythmic therapy aimed at slowing the ventricular response is indicated. One or more of these pharmacological agents may be used:

- i. Intravenous amiodarone.<sup>162</sup> (*Level of Evidence: C*)
- ii. Intravenous digoxin for rate control principally for patients with severe LV dysfunction and heart failure. (*Level of Evidence: C*)

2. Sustained atrial fibrillation and atrial flutter in patients with ongoing ischemia but without hemodynamic compromise should be treated with one or more of the following:

- a. Beta-adrenergic blockade is preferred, unless contraindicated. (*Level of Evidence: C*)
- b. Intravenous diltiazem or verapamil. (*Level of Evidence: C*)
- c. Synchronized cardioversion with an initial monophasic shock of 200 J for atrial fibrillation and 50 J for flutter, preceded by brief general anesthesia or conscious sedation whenever possible. (*Level of Evidence: C*)
3. For episodes of sustained atrial fibrillation or flutter without hemodynamic compromise or ischemia, rate control is indicated. In addition, patients with sustained atrial fibrillation or flutter should be given anticoagulant therapy. Consideration should be given to cardioversion to sinus rhythm in patients with a history of atrial fibrillation or flutter prior to STEMI. (*Level of Evidence: C*)

4. Reentrant paroxysmal supraventricular tachycardia, because of its rapid rate, should be treated with the following in the sequence shown:

- a. Carotid sinus massage. (*Level of Evidence: C*)
- b. Intravenous adenosine (6 mg × 1 over 1 to 2 seconds; if no response, 12 mg IV after 1 to 2 minutes may be given; repeat 12 mg dose if needed. (*Level of Evidence: C*)
- c. Intravenous beta-adrenergic blockade with metoprolol (2.5 to 5.0 mg every 2 to 5 minutes to a total of 15 mg over 10 to 15 minutes) or atenolol (2.5 to 5.0 mg over 2 minutes to a total of 10 mg in 10 to 15 minutes). (*Level of Evidence: C*)
- d. Intravenous diltiazem (20 mg [0.25 mg/kg]) over 2 minutes followed by an infusion of 10 mg/h. (*Level of Evidence: C*)
- e. Intravenous digoxin, recognizing that there may be a delay of at least 1 hour before pharmacological effects appear (8 to 15 mcg/kg [0.6 to 1.0 mg in a person weighing 70 kg]). (*Level of Evidence: C*)

##### *Class III*

1. Treatment of atrial premature beats is not indicated. (*Level of Evidence: C*)

See the full-text guidelines for discussion.

#### *3. Bradyarrhythmias*

See Table 3 for recommendations.

**TABLE 3.** Recommendations for Treatment of Atrioventricular and Intraventricular Conduction Disturbances During STEMI

Atrioventricular Conduction														
Intraventricular Conduction	First-Degree AV Block						Mobitz I Second-Degree AV Block				Mobitz II Second-Degree AV Block			
	Normal		Anterior MI		Nonanterior MI		Anterior MI		Nonanterior MI		Anterior MI		Nonanterior MI	
Normal	Action	Class	Action	Class	Action	Class	Action	Class	Action	Class	Action	Class	Action	Class
	Observe	I	Observe	I	Observe	I	Observe	IIb	Observe	IIa	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	III	TC	IIb	TC	IIb	TC	I	TC	I	TC	I	TC	I
	TV	III	TV	III	TV	III	TV	III	TV	III	TV	IIa	TV	IIa
Old or new fascicular block (LAFB or LPFB)	Observe	I	Observe	IIb	Observe	IIb	Observe	IIb	Observe	IIb	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	IIb	TC	I	TC	IIa	TC	I	TC	I	TC	I	TC	I
	TV	III	TV	III	TV	III	TV	III	TV	III	TV	IIa	TV	IIb
Old bundle-branch block	Observe	I	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	IIb	TC	I	TC	I	TC	I	TC	I	TC	I	TC	I
	TV	III	TV	IIb	TV	IIb	TV	IIb	TV	IIb	TV	IIa	TV	IIa
New bundle-branch block	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	I	TC	I	TC	I	TC	I	TC	I	TC	IIb	TC	IIb
	TV	IIb	TV	IIa	TV	IIa	TV	IIa	TV	IIa	TV	I	TV	I
Fascicular block + RBBB	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	I	TC	I	TC	I	TC	I	TC	I	TC	IIb	TC	IIb
	TV	IIb	TV	IIa	TV	IIa	TV	IIa	TV	IIa	TV	I	TV	I
Alternating left and right bundle-branch block	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III	Observe	III
	A	III	A	III	A	III	A*	III	A	III	A	III	A	III
	TC	IIb	TC	IIb	TC	IIb	TC	IIb	TC	IIb	TC	IIb	TC	IIb
	TV	I	TV	I	TV	I	TV	I	TV	I	TV	I	TV	I

This table is designed to summarize the atrioventricular (column headings) and intraventricular (row headings) conduction disturbances that may occur during acute anterior or nonanterior STEMI, the possible treatment options, and the indications for each possible therapeutic option.

LAFB indicates left anterior fascicular block; LPFB, left posterior fascicular block; RBBB, right bundle-branch block; A, atropine; TC, transcutaneous pacing; TV, temporary transvenous pacing; STEMI, ST elevation myocardial infarction; AV, atrioventricular; and MI, myocardial infarction.

#### Action

There are 4 possible actions, or therapeutic options, listed and classified for each bradyarrhythmia or conduction problem:

1. Observe: continued ECG monitoring, no further action planned.
2. A, and A\*: atropine administered at 0.6 to 1.0 mg IV every 5 minutes to up to 0.04 mg/kg. In general, because the increase in sinus rate with atropine is unpredictable, this is to be avoided unless there is symptomatic bradycardia that will likely respond to a vagolytic agent, such as sinus bradycardia or Mobitz I, as denoted by the asterisk, above.
3. TC: application of transcutaneous pads and standby transcutaneous pacing with no further progression to transvenous pacing imminently planned.
4. TV: temporary transvenous pacing. It is assumed, but not specified in the table, that at the discretion of the clinician, transcutaneous pads will be applied and standby transcutaneous pacing will be in effect as the patient is transferred to the fluoroscopy unit for temporary transvenous pacing.

#### Class

Each possible therapeutic option is further classified according to ACC/AHA criteria as I, IIa, IIb, and III.

#### Level of Evidence

This table was developed from (1) published observational case reports and case series, (2) published summaries, not meta-analyses, of these data; and (3) expert opinion, largely from the preperfusion era. There are no published randomized trials comparing different strategies of managing conduction disturbances after STEMI. Thus, the level of evidence for the recommendations in this table is C.

#### How to Use the Table

Example: 54-year-old man is admitted with an anterior STEMI and a narrow QRS on admission. On day 1, he develops a right bundle-branch block (RBBB), with a PR interval of 0.28 seconds.

1. RBBB is an intraventricular conduction disturbance, so look at row 'New bundle-branch block.'
2. Find the column for 'First-Degree AV Block.'
3. Find the 'Action' and 'Class' cells at the convergence.
4. Note that "Observe" and "Atropine" are class III, not indicated; transcutaneous pacing (TC) is class I. Temporary transvenous pacing (TV) is class IIb.

*a. Acute Treatment of Conduction Disturbances and Bradyarrhythmias*

VENTRICULAR ASYSTOLE

*Class I*

1. Prompt resuscitative measures, including chest compressions, atropine, vasopressin, epinephrine, and temporary pacing, should be administered to treat ventricular asystole. (*Level of Evidence: B*)

*b. Use of Permanent Pacemakers*

PERMANENT PACING FOR BRADYCARDIA OR CONDUCTION BLOCKS ASSOCIATED WITH STEMI

*Class I*

1. Permanent ventricular pacing is indicated for persistent second-degree AV block in the His-Purkinje system with bilateral bundle-branch block or third-degree AV block within or below the His-Purkinje system after STEMI. (*Level of Evidence: B*)
2. Permanent ventricular pacing is indicated for transient advanced second- or third-degree infranodal AV block and associated bundle-branch block. If the site of block is uncertain, an electrophysiological study may be necessary. (*Level of Evidence: B*)
3. Permanent ventricular pacing is indicated for persistent and symptomatic second- or third-degree AV block. (*Level of Evidence: C*)

*Class IIb*

1. Permanent ventricular pacing may be considered for persistent second- or third-degree AV block at the AV node level. (*Level of Evidence: B*)

*Class III*

1. Permanent ventricular pacing is not recommended for transient AV block in the absence of intraventricular conduction defects. (*Level of Evidence: B*)
2. Permanent ventricular pacing is not recommended for transient AV block in the presence of isolated left anterior fascicular block. (*Level of Evidence: B*)
3. Permanent ventricular pacing is not recommended for acquired left anterior fascicular block in the absence of AV block. (*Level of Evidence: B*)
4. Permanent ventricular pacing is not recommended for persistent first-degree AV block in the presence of bundle-branch block that is old or of indeterminate age. (*Level of Evidence: B*)

Indications for permanent pacing after STEMI in patients experiencing AV block are related in large measure to the presence of intraventricular conduction defects (Table 3). Unlike some other indications for permanent pacing, the criteria for patients with STEMI and AV block do not necessarily depend on the presence of symptoms. Furthermore, the requirement for temporary pacing in STEMI does not by itself constitute an indication for permanent pacing.<sup>163</sup>

SINUS NODE DYSFUNCTION AFTER STEMI

*Class I*

1. Symptomatic sinus bradycardia, sinus pauses greater than 3 seconds, or sinus bradycardia with a heart rate less than 40 bpm and associated hypotension or signs of systemic hemodynamic compromise should be treated with an intravenous bolus of atropine 0.6 to 1.0 mg. If bradycardia is persistent and maximal (2 mg) doses of atropine have been used, transcutaneous or transvenous (preferably atrial) temporary pacing should be instituted. (*Level of Evidence: C*)

The published ACC/AHA Guidelines<sup>164</sup> for Implantation of Pacemakers should be used to guide therapy in STEMI patients with persistent sinus node dysfunction.

PACING MODE SELECTION IN STEMI PATIENTS

*Class I*

1. All patients who have an indication for permanent pacing after STEMI should be evaluated for ICD indications. (*Level of Evidence: C*)

*Class IIa*

1. It is reasonable to implant a permanent dual-chamber pacing system in STEMI patients who need permanent pacing and are in sinus rhythm. It is reasonable that patients in permanent atrial fibrillation or flutter receive a single-chamber ventricular device. (*Level of Evidence: C*)
2. It is reasonable to evaluate all patients who have an indication for permanent pacing after STEMI for biventricular pacing (cardiac resynchronization therapy). (*Level of Evidence: C*)

When a permanent pacemaker is being considered for a post-STEMI patient, the clinician should address 2 additional questions regarding the patient: is there an indication for biventricular pacing, and is there an indication for ICD use?<sup>165</sup> The algorithm to define whether an ICD is indicated is contained in Figure 5.

H. Recurrent Chest Pain After STEMI

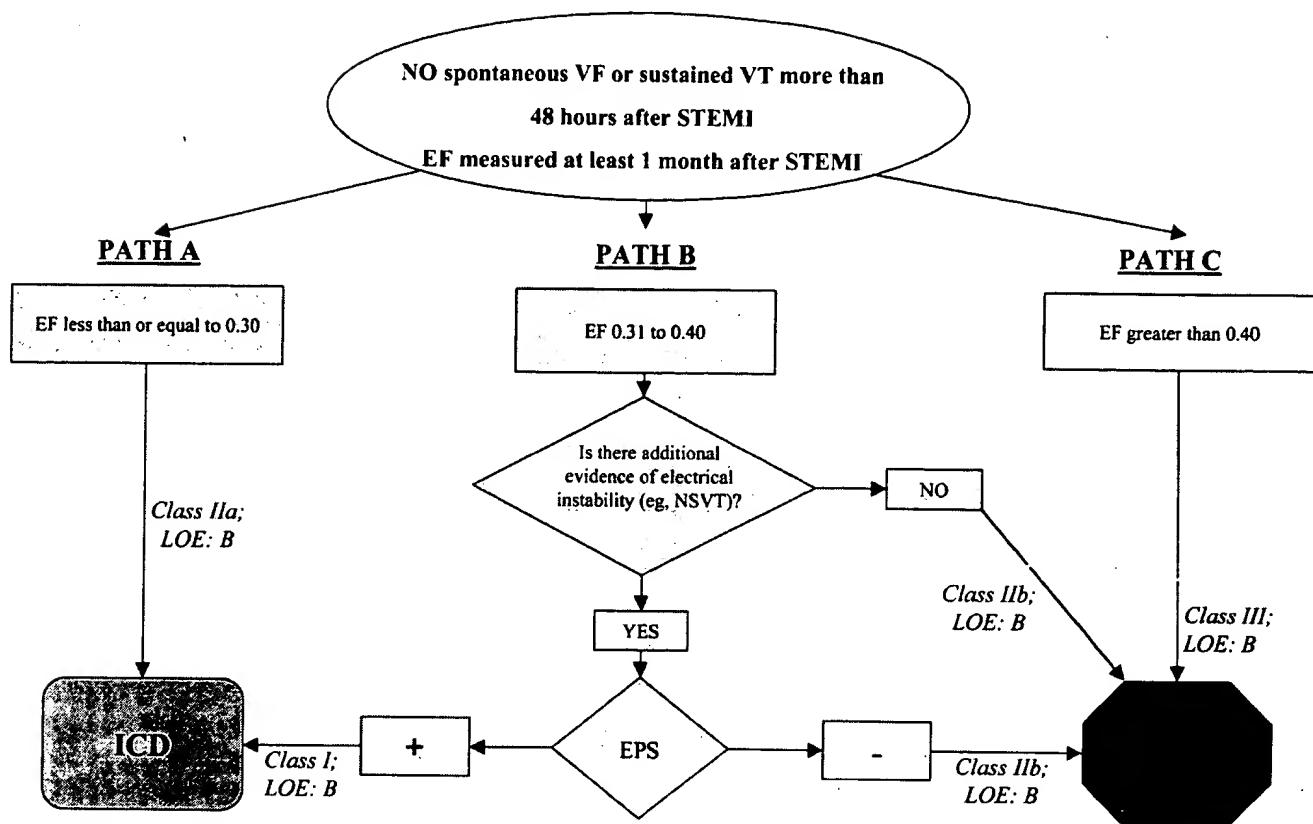
*I. Pericarditis*

*Class I*

1. Aspirin is recommended for treatment of pericarditis after STEMI. Doses as high as 650 mg orally (enteric) every 4 to 6 hours may be needed. (*Level of Evidence: B*)
2. Anticoagulation should be immediately discontinued if pericardial effusion develops or increases. (*Level of Evidence: C*)

*Class IIa*

1. For episodes of pericarditis after STEMI that are not adequately controlled with aspirin, it is reasonable to administer 1 or more of the following:
  - a. Colchicine 0.6 mg every 12 hours orally. (*Level of Evidence: B*)
  - b. Acetaminophen 500 mg orally every 6 hours. (*Level of Evidence: C*)



**Figure 5.** Algorithm to aid in selection of ICD in patients with STEMI and diminished ejection fraction (EF). Appropriate management path is selected based on LVEF measured at least 1 month after STEMI. These criteria, which are based on published data, form the basis for the full-text guidelines in Section 7.7.1.5. All patients, whether an ICD is implanted or not, should receive medical therapy as outlined in the guidelines. VF indicates ventricular fibrillation; VII, ventricular tachycardia; STEMI, ST-elevation myocardial infarction; NSVT, nonsustained VT; LOE, level of evidence; EPS, electrophysiological studies; LVEF, left ventricular EF.

#### Class IIb

1. Nonsteroidal anti-inflammatory drugs may be considered for pain relief; however, they should not be used for extended periods because of their continuous effect on platelet function, an increased risk of myocardial scar thinning, and infarct expansion. (*Level of Evidence: B*)
2. Corticosteroids might be considered only as a last resort in patients with pericarditis refractory to aspirin or nonsteroidal drugs. Although corticosteroids are effective for pain relief, their use is associated with an increased risk of scar thinning and myocardial rupture. (*Level of Evidence: C*)

#### Class III

1. Ibuprofen should not be used for pain relief because it blocks the antiplatelet effect of aspirin and can cause myocardial scar thinning and infarct expansion. (*Level of Evidence: B*)

#### 2. Recurrent Ischemia/Infarction

#### Class I

1. Patients with recurrent ischemic-type chest discomfort after initial reperfusion therapy for STEMI should undergo escalation of medical therapy with nitrates and beta-blockers to decrease myocardial oxygen demand and reduce ische-

mia. Intravenous anticoagulation should be initiated if not already accomplished. (*Level of Evidence: B*)

2. In addition to escalation of medical therapy, patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor LV function, or a large area of myocardium at risk should be referred urgently for cardiac catheterization and undergo revascularization as needed. Insertion of an IABP should also be considered. (*Level of Evidence: C*)
3. Patients with recurrent ischemic-type chest discomfort who are considered candidates for revascularization should undergo coronary angiography and PCI or CABG as dictated by coronary anatomy. (*Level of Evidence: B*)

#### Class IIa

1. It is reasonable to (re)administer fibrinolytic therapy to patients with recurrent ST elevation and ischemic-type chest discomfort who are not considered candidates for revascularization or for whom coronary angiography and PCI cannot be rapidly (ideally within 60 minutes from the onset of recurrent discomfort) implemented. (*Level of Evidence: C*)

#### Class III

1. Streptokinase should not be readministered to treat recurrent ischemia/infarction in patients who received a non-fibrin-specific fibrinolytic agent more than 5 days

previously to treat the acute STEMI event. (*Level of Evidence: C*)

Patients with recurrent ischemic-type chest discomfort should undergo escalation of medical therapy that includes beta-blockers (intravenously and then orally) and nitrates (sublingually and then intravenously); consideration should be given to initiation of intravenous anticoagulation if the patient is not already therapeutically anticoagulated. Secondary causes of recurrent ischemia, such as poorly controlled heart failure, anemia, and arrhythmias, should be corrected.

## I. Other Complications

### 1. Ischemic Stroke

#### *Class I*

1. Neurological consultation should be obtained in STEMI patients who have an acute ischemic stroke. (*Level of Evidence: C*)
2. STEMI patients who have an acute ischemic stroke should be evaluated with echocardiography, neuroimaging, and vascular imaging studies to determine the cause of the stroke. (*Level of Evidence: C*)
3. STEMI patients with acute ischemic stroke and persistent atrial fibrillation should receive lifelong moderate-intensity (international normalized ratio [INR] 2 to 3) warfarin therapy. (*Level of Evidence: A*)
4. STEMI patients with or without acute ischemic stroke who have a cardiac source of embolism (atrial fibrillation, mural thrombus, or akinetic segment) should receive moderate-intensity (INR 2 to 3) warfarin therapy (in addition to aspirin). The duration of warfarin therapy should be dictated by clinical circumstances (eg, at least 3 months for patients with an LV mural thrombus or akinetic segment and indefinitely in patients with persistent atrial fibrillation). The patient should receive LMWH or UFH until adequately anticoagulated with warfarin. (*Level of Evidence: B*)

#### *Class IIa*

1. It is reasonable to assess the risk of ischemic stroke in patients with STEMI. (*Level of Evidence: A*)
2. It is reasonable that STEMI patients with nonfatal acute ischemic stroke receive supportive care to minimize complications and maximize functional outcome. (*Level of Evidence: C*)

#### *Class IIb*

1. Carotid angioplasty/stenting, 4 to 6 weeks after ischemic stroke, might be considered in STEMI patients who have an acute ischemic stroke attributable to an internal carotid artery–origin stenosis of at least 50% and who have a high surgical risk of morbidity/mortality early after STEMI. (*Level of Evidence: C*)

An algorithm for evaluation and antithrombotic therapy for ischemic stroke is shown in Figure 35 of the full-text guideline.

### 2. DVT and Pulmonary Embolism

#### *Class I*

1. DVT or pulmonary embolism after STEMI should be treated with full-dose LMWH for a minimum of 5 days and until the patient is adequately anticoagulated with warfarin. Start warfarin concurrently with LMWH and titrate to INR of 2 to 3. (*Level of Evidence: A*)
2. Patients with CHF after STEMI who are hospitalized for prolonged periods, unable to ambulate, or considered at high risk for DVT and are not otherwise anticoagulated should receive low-dose heparin prophylaxis, preferably with LMWH. (*Level of Evidence: A*)

### J. CABG Surgery After STEMI

#### 1. Timing of Surgery

#### *Class IIa*

1. In patients who have had a STEMI, CABG mortality is elevated for the first 3 to 7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. Patients who have been stabilized (no ongoing ischemia, hemodynamic compromise, or life-threatening arrhythmia) after STEMI and who have incurred a significant fall in LV function should have their surgery delayed to allow myocardial recovery to occur. If critical anatomy exists, revascularization should be undertaken during the index hospitalization. (*Level of Evidence: B*)

The Writing Committee believes that if stable STEMI patients with preserved LV function require surgical revascularization, then CABG can be undertaken within several days of the infarction without an increased risk.

#### 2. Arterial Grafting

#### *Class I*

1. An internal mammary artery graft to a significantly stenosed left anterior descending coronary artery should be used whenever possible in patients undergoing CABG after STEMI. (*Level of Evidence: B*)

#### 3. CABG for Recurrent Ischemia After STEMI

#### *Class I*

1. Urgent CABG is indicated if the coronary angiogram reveals anatomy that is unsuitable for PCI. (*Level of Evidence: B*)

#### 4. Elective CABG Surgery After STEMI in Patients With Angina

#### *Class I*

1. CABG is recommended for patients with stable angina who have significant left main coronary artery stenosis. (*Level of Evidence: A*)
2. CABG is recommended for patients with stable angina who have left main equivalent disease: significant (at least 70%) stenosis of the proximal left anterior de-

scending coronary artery and proximal left circumflex artery. (*Level of Evidence: A*)

3. CABG is recommended for patients with stable angina who have 3-vessel disease (Survival benefit is greater when LVEF is less than 0.50). (*Level of Evidence: A*)
4. CABG is beneficial for patients with stable angina who have 1- or 2-vessel coronary disease without significant proximal left anterior descending coronary artery stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*Level of Evidence: B*)
5. CABG is recommended in patients with stable angina who have 2-vessel disease with significant proximal left anterior descending coronary artery stenosis and either ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. (*Level of Evidence: A*)

The role of surgical revascularization has been reviewed extensively in the ACC/AHA Guidelines for CABG Surgery.<sup>166</sup> Consideration for revascularization after STEMI includes PCI and CABG. Providers should individualize patient management on the basis of clinical circumstances, available revascularization options, and patient preference.

#### **5. CABG Surgery After STEMI and Antiplatelet Agents**

##### **Class I**

1. Aspirin should not be withheld before elective or nonelective CABG after STEMI. (*Level of Evidence: C*)
2. Aspirin (75 to 325 mg daily) should be prescribed as soon as possible (within 24 hours) after CABG unless contraindicated. (*Level of Evidence: B*)
3. In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days. (*Level of Evidence: B*)

STEMI patients undergoing revascularization frequently receive 1 or more antiplatelet agents and heparin, all of which may increase risk of serious bleeding during and after cardiac surgery. Delaying surgery until platelet function has recovered may not be feasible in many circumstances. In patients treated with the small-molecule GP IIb/IIIa receptor antagonists, tirofiban and eptifibatide, platelet function returns toward normal within 4 hours of stopping treatment. Platelet aggregation does not return toward normal for more than 48 hours in patients treated with abciximab. Management strategies, other than delaying surgery, include platelet transfusions for patients who were recently treated with abciximab, reduced heparin dosing during cardiopulmonary bypass, and possible use of antifibrinolytic agents such as aprotinin or tranexamic acid.<sup>167</sup> Because clopidogrel, when added to aspirin, increases the risk of bleeding during major surgery in patients who are scheduled for elective CABG, clopidogrel should be withheld for at least 5 days<sup>168</sup> and preferably for 7 days before surgery.<sup>169</sup>

#### **K. Convalescence, Discharge, and Post-MI Care**

##### **I. Risk Stratification at Hospital Discharge**

The risk stratification approach for decision-making about catheterization is described in Figure 6. The suggested

algorithm for electrophysiological testing and ICD placement is shown in Figure 5.

##### **a. Role of Exercise Testing**

##### **Class I**

1. Exercise testing should be performed either in the hospital or early after discharge in STEMI patients not selected for cardiac catheterization and without high-risk features to assess the presence and extent of inducible ischemia. (*Level of Evidence: B*)
2. In patients with baseline abnormalities that compromise ECG interpretation, echocardiography or myocardial perfusion imaging should be added to standard exercise testing. (*Level of Evidence: B*)

##### **Class IIb**

1. Exercise testing might be considered before discharge of patients recovering from STEMI to guide the post-discharge exercise prescription or to evaluate the functional significance of a coronary lesion previously identified at angiography. (*Level of Evidence: C*)

##### **Class III**

1. Exercise testing should not be performed within 2 to 3 days of STEMI in patients who have not undergone successful reperfusion. (*Level of Evidence: C*)
2. Exercise testing should not be performed to evaluate patients with STEMI who have unstable postinfarction angina, decompensated CHF, life-threatening cardiac arrhythmias, noncardiac conditions that severely limit their ability to exercise, or other absolute contraindications to exercise testing.<sup>170</sup> (*Level of Evidence: C*)
3. Exercise testing should not be used for risk stratification in patients with STEMI who have already been selected for cardiac catheterization. (*Level of Evidence: C*)

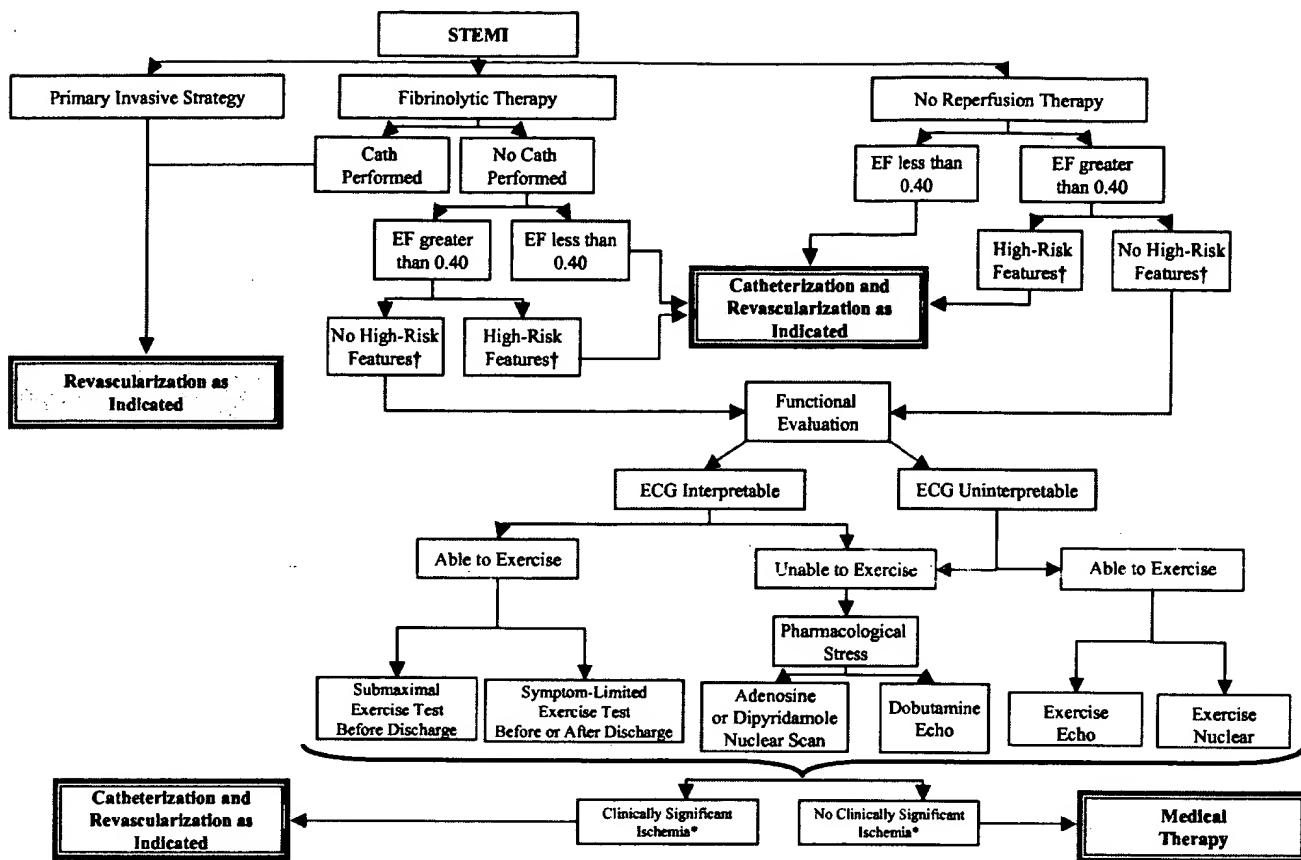
Exercise testing after STEMI may be performed to (1) assess functional capacity and the patient's ability to perform tasks at home and at work; (2) establish exercise parameters for cardiac rehabilitation; (3) evaluate the efficacy of the patient's current medical regimen; (4) risk-stratify the post-STEMI patient according to the likelihood of a subsequent cardiac event;<sup>171–175</sup> (5) evaluate chest pain symptoms after STEMI; and (6) provide reassurance to patients regarding their functional capacity after STEMI as a guide to returning to work.

##### **b. Role of Echocardiography**

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses the role of echocardiography. (See Sections 7.11.1.3, 7.11.1.4, and 7.11.1.5 of the full-text guidelines for additional discussion on imaging considerations.)

##### **Class I**

1. Echocardiography should be used in patients with STEMI not undergoing LV angiography to assess baseline LV function, especially if the patient is hemodynamically unstable. (*Level of Evidence: C*)



**Figure 6.** Evidence-based approach to need for catheterization (cath) and revascularization after STEMI. This algorithm shows treatment paths for patients who initially undergo a primary invasive strategy, receive fibrinolytic therapy, or do not undergo reperfusion therapy for STEMI. Patients who have not undergone a primary invasive strategy and have no high-risk features should undergo functional evaluation with one of the noninvasive tests shown. When clinically significant ischemia is detected, patients should undergo catheterization and revascularization as indicated; if no clinically significant ischemia is detected, medical therapy is prescribed after STEMI. \*Please see Table 23 of the ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina for further definition. †Please see Table 3, Section 6.3.1.6.2., and Section 7.3. in the full-text STEMI guidelines for further discussion. STEMI indicates ST-elevation myocardial infarction; EF, ejection fraction; ECG, electrocardiography.

2. Echocardiography should be used to evaluate patients with inferior STEMI, clinical instability, and clinical suspicion of RV infarction. (See ACC/AHA Guidelines for Clinical Application of Echocardiography.<sup>153</sup>) (*Level of Evidence: C*)
3. Echocardiography should be used in patients with STEMI to evaluate suspected complications, including acute MR, cardiogenic shock, infarct expansion, VSR, intracardiac thrombus, and pericardial effusion. (*Level of Evidence: C*)
4. Stress echocardiography (or myocardial perfusion imaging) should be used in patients with STEMI for in-hospital or early postdischarge assessment for inducible ischemia when baseline abnormalities are expected to compromise ECG interpretation. (*Level of Evidence: C*)

#### Class IIa

1. Echocardiography is reasonable in patients with STEMI to re-evaluate ventricular function during recovery when results are used to guide therapy. (*Level of Evidence: C*)
2. Dobutamine echocardiography (or myocardial perfusion imaging) is reasonable in hemodynamically and electrically stable patients 4 or more days after STEMI

to assess myocardial viability when required to define the potential efficacy of revascularization. (*Level of Evidence: C*)

3. In STEMI patients who have not undergone contrast ventriculography, echocardiography is reasonable to assess ventricular function after revascularization. (*Level of Evidence: C*)

#### Class III

1. Echocardiography should not be used for early routine reevaluation in patients with STEMI in the absence of any change in clinical status or revascularization procedure. Reassessment of LV function 30 to 90 days later may be reasonable. (*Level of Evidence: C*)

The use of echocardiography in STEMI is discussed in detail in the ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography.<sup>153</sup>

#### c. Exercise Myocardial Perfusion Imaging

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses the role of exercise myocardial perfusion

imaging. (See Sections 7.11.1.2, 7.11.1.4, and 7.11.1.5 of the full-text guidelines for additional discussion on imaging considerations.)

#### **Class I**

1. Dipyridamole or adenosine stress perfusion nuclear scintigraphy or dobutamine echocardiography before or early after discharge should be used in patients with STEMI who are not undergoing cardiac catheterization to look for inducible ischemia in patients judged to be unable to exercise. (*Level of Evidence: B*)

#### **Class IIa**

1. Myocardial perfusion imaging or dobutamine echocardiography is reasonable in hemodynamically and electrically stable patients 4 to 10 days after STEMI to assess myocardial viability when required to define the potential efficacy of revascularization. (*Level of Evidence: C*)

Recommended strategies for exercise test evaluations after STEMI are presented in Figure 6. These strategies and the data on which they are based are reviewed in more detail in the ACC/AHA 2002 Guideline Update for Exercise Testing.<sup>170</sup>

#### *d. LV Function*

Noninvasive imaging in patients recovering from STEMI includes echocardiography and radionuclide imaging. This section discusses the importance of measurement of LV function. Either of the above imaging techniques can provide clinically useful information.

#### **Class I**

1. LVEF should be measured in all STEMI patients. (*Level of Evidence: B*)

Assessment of LV function after STEMI has been shown to be one of the most accurate predictors of future cardiac events in both the prereperfusional<sup>176</sup> and the reperfusion eras.<sup>177,178</sup> Multiple techniques for assessing LV function of patients after STEMI have important prognostic value. Because of the dynamic nature of LV function recovery after STEMI, clinicians should consider the timing of the imaging study relative to the index event when assessing LV function. (See Table 6 of the ACC/AHA/ASE 2003 Guideline Update on the Clinical Application of Echocardiography for further discussion of the impact of timing on assessment of LV function and inducible ischemia.)<sup>153</sup>

#### *e. Invasive Evaluation*

#### **Class I**

1. Coronary arteriography should be performed in patients with spontaneous episodes of myocardial ischemia or episodes of myocardial ischemia provoked by minimal exertion during recovery from STEMI. (*Level of Evidence: A*)
2. Coronary arteriography should be performed for intermediate- or high-risk findings on noninvasive testing after STEMI (see Table 23 of the ACC/AHA

2002 Guideline Update for the Management of Patients With Chronic Stable Angina).<sup>179</sup> (*Level of Evidence: B*)

3. Coronary arteriography should be performed if the patient is sufficiently stable before definitive therapy of a mechanical complication of STEMI, such as acute MR, VSR, pseudoaneurysm, or LV aneurysm. (*Level of Evidence: B*)
4. Coronary arteriography should be performed in patients with persistent hemodynamic instability. (*Level of Evidence: B*)
5. Coronary arteriography should be performed in survivors of STEMI who had clinical heart failure during the acute episode but subsequently demonstrated well-preserved LV function. (*Level of Evidence: C*)

#### **Class IIa**

1. It is reasonable to perform coronary arteriography when STEMI is suspected to have occurred by a mechanism other than thrombotic occlusion of an atherosclerotic plaque. This would include coronary embolism, certain metabolic or hematological diseases, or coronary artery spasm. (*Level of Evidence: C*)
2. Coronary arteriography is reasonable in STEMI patients with any of the following: diabetes mellitus, LVEF less than 0.40, CHF, prior revascularization, or life-threatening ventricular arrhythmias. (*Level of Evidence: C*)

#### **Class IIb**

1. Catheterization and revascularization may be considered as part of a strategy of routine coronary arteriography for risk assessment after fibrinolytic therapy (See Section 6.3.1.6.4.7 of the full-text guidelines). (*Level of Evidence: B*)

#### **Class III**

1. Coronary arteriography should not be performed in survivors of STEMI who are thought not to be candidates for coronary revascularization. (*Level of Evidence: A*)

The Writing Committee encourages contemporary research into the benefit of routine catheterization versus watchful waiting after fibrinolytic therapy in the contemporary era.<sup>180</sup> (See Section 6.3.1.6.4.7 of the full-text guidelines)

#### *f. Assessment of Ventricular Arrhythmias*

#### **Class IIb**

1. Noninvasive assessment of the risk of ventricular arrhythmias may be considered (including signal-averaged ECG, 24-hour ambulatory monitoring, heart rate variability, micro T-wave alternans, and T-wave variability) in patients recovering from STEMI. (*Level of Evidence: B*)

The clinical applicability of these tests to the post-STMI patient is in a state of evolution. Until these issues are resolved, use these tests are used only to support routine management and risk assessment.

## L. Secondary Prevention

### *Class I*

1. Patients who survive the acute phase of STEMI should have plans initiated for secondary prevention therapies. (*Level of Evidence: A*)

Secondary prevention therapies, unless contraindicated, are an essential part of the management of all patients with STEMI (Table 4),<sup>181</sup> regardless of sex.<sup>182,183</sup> Inasmuch as atherosclerotic vascular disease is frequently found in multiple vascular beds, the physician should search for symptoms or signs of peripheral vascular disease or cerebrovascular disease in patients presenting with STEMI.

### *1. Patient Education Before Discharge*

#### *Class I*

1. Before hospital discharge, all STEMI patients should be educated about and actively involved in planning for adherence to the lifestyle changes and drug therapies that are important for the secondary prevention of cardiovascular disease. (*Level of Evidence: B*)
2. Post-STEMI patients and their family members should receive discharge instructions about recognizing acute cardiac symptoms and appropriate actions to take in response (ie, calling 9-1-1 if symptoms are unimproved or worsening 5 minutes after onset, or if symptoms are unimproved or worsening 5 minutes after 1 sublingual nitroglycerin dose) to ensure early evaluation and treatment should symptoms recur. (*Level of Evidence: C*)
3. Family members of STEMI patients should be advised to learn about AEDs and CPR and be referred to a CPR training program. Ideally, such training programs would have a social support component targeting family members of high-risk patients. (*Level of Evidence: C*)

### *2. Lipid Management*

#### *Class I*

1. Dietary therapy that is low in saturated fat and cholesterol (less than 7% of total calories as saturated fat and less than 200 mg/dL cholesterol) should be started on discharge after recovery from STEMI. Increased consumption of the following should be encouraged: omega-3 fatty acids, fruits, vegetables, soluble (viscous) fiber, and whole grains. Calorie intake should be balanced with energy output to achieve and maintain a healthy weight. (*Level of Evidence: A*)
2. A lipid profile should be obtained from past records, but if not available, it should be performed in all patients with STEMI, preferably after they have fasted and within 24 hours of admission. (*Level of Evidence: C*)
3. The target LDL-C level after STEMI should be substantially less than 100 mg/dL. (*Level of Evidence: A*)
  - a. Patients with LDL-C 100 mg/dL or above should be prescribed drug therapy on hospital discharge, with preference given to statins. (*Level of Evidence: A*)
  - b. Patients with LDL-C less than 100 mg/dL or unknown LDL-C levels should be prescribed statin therapy on hospital discharge. (*Level of Evidence: B*)

4. Patients with non-high-density lipoprotein cholesterol (non HDL-C) levels less than 130 mg/dL who have an HDL-C level less than 40 mg/dL should receive special emphasis on nonpharmacological therapy (eg, exercise, weight loss, and smoking cessation) to increase HDL-C. (*Level of Evidence: B*)

#### *Class IIa*

1. It is reasonable to prescribe drug therapy at discharge to patients with non-HDL-C greater than or equal to 130 mg/dL, with a goal of reducing non-HDL-C to substantially less than 130 mg/dL. (*Level of Evidence: B*)
2. It is reasonable to prescribe drug therapy such as niacin or fibrate therapy to raise HDL-C levels in patients with LDL-C less than 100 mg/dL and non-HDL-C less than 130 mg/dL but HDL-C less than 40 mg/dL despite dietary and other nonpharmacological therapy. (*Level of Evidence: B*) Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician.
3. It is reasonable to add drug therapy with either niacin or a fibrate to diet regardless of LDL-C and HDL-C levels when triglyceride levels are greater than 500 mg/dL. In this setting, non-HDL-C (goal substantially less than 130 mg/dL) should be the cholesterol target rather than LDL-C. (*Level of Evidence: B*) Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician.

Early secondary prevention trials conducted before the use of statin therapy, which used then-available drugs and diet to lower cholesterol, demonstrated significant reductions of 25% in nonfatal MIs and 14% in fatal MIs.<sup>14</sup> Subsequently, a growing body of evidence, mainly from large randomized clinical trials of statin therapy, has firmly established the desirability of lowering atherogenic serum lipids in patients who have recovered from a STEMI. See Table 4 for additional discussion of recommendations.

### *3. Weight Management*

#### *Class I*

1. Measurement of waist circumference and calculation of body mass index are recommended. Desirable body mass index range is 18.5 to 24.9 kg/m<sup>2</sup>. A waist circumference greater than 40 inches in men and 35 inches in women would result in evaluation for metabolic syndrome and implementation of weight-reduction strategies. (*Level of Evidence: B*)
2. Patients should be advised about appropriate strategies for weight management and physical activity (usually accomplished in conjunction with cardiac rehabilitation). (*Level of Evidence: B*)
3. A plan should be established to monitor the response of body mass index and waist circumference to therapy (usually accomplished in conjunction with cardiac rehabilitation). (*Level of Evidence: B*)

**TABLE 4. Secondary Prevention for STEMI Patients**

Goals	Intervention Recommendations
<b>Smoking:</b> Goal complete cessation	Assess tobacco use. Strongly encourage patient and family to stop smoking and to avoid secondhand smoke. Provide counseling, pharmacological therapy (including nicotine replacement and bupropion), and formal smoking cessation programs as appropriate.
<b>Blood pressure control:</b> Goal Less than 140/90 mm Hg or Less than 130/80 mm Hg if chronic kidney disease or diabetes	If blood pressure is 120/80 mm Hg or greater: <ul style="list-style-type: none"> <li>Initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients.</li> <li>If blood pressure is 140/90 mm Hg or greater or 130/80 mm Hg or greater for individuals with chronic kidney disease or diabetes:</li> <li>Add blood pressure medications, emphasizing the use of beta-blockers and inhibition of the renin-angiotensin-aldosterone system.</li> </ul>
<b>Lipid management:</b> TG less than 200 mg/dL <b>Primary goal</b> LDL-C substantially less than 100 mg/dL	Start dietary therapy in all patients (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol). Promote physical activity and weight management. Encourage increased consumption of omega-3 fatty acids. Assess fasting lipid profile in all patients, preferably within 24 hours of STEMI. Add drug therapy according to the following guide: <ul style="list-style-type: none"> <li>LDL-C substantially less than 100 mg/dL (baseline or on-treatment): <ul style="list-style-type: none"> <li>Statins should be used to lower LDL-C.</li> </ul> </li> <li>LDL-C greater than or equal to 100 mg/dL (baseline or on-treatment): <ul style="list-style-type: none"> <li>Intensify LDL-C-lowering therapy with drug treatment, giving preference to statins.</li> </ul> </li> </ul>
<b>Lipid management:</b> TG 200 mg/dL or greater <b>Primary goal</b> Non-HDL-C* substantially less than 130 mg/dL	If TG is greater than or equal to 150 mg/dL or HDL-C is less than 40 mg/dL: <ul style="list-style-type: none"> <li>Emphasize weight management and physical activity. Advise smoking cessation.</li> </ul> If TG is 200 to 499 mg/dL: <ul style="list-style-type: none"> <li>After LDL-C-lowering therapy,† consider adding fibrate or niacin.‡</li> </ul> If TG is greater than or equal to 500 mg/dL: <ul style="list-style-type: none"> <li>Consider fibrate or niacin‡ before LDL-C-lowering therapy.†</li> <li>Consider omega-3 fatty acids as adjunct for high TG.</li> </ul>
<b>Physical activity:</b> Minimum goal 30 minutes 3 to 4 days per week; Optimal daily	Assess risk, preferably with exercise test, to guide prescription. Encourage minimum of 30 to 60 minutes of activity, preferably daily, or at least 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work). Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted.
<b>Weight management:</b> Goal BMI 18.5–24.9 kg/m <sup>2</sup> Waist circumference: Women: Less than 35 inches Men: Less than 40 inches	Calculate BMI and measure waist circumference as part of evaluation. Monitor response of BMI and waist circumference to therapy. Start weight management and physical activity as appropriate. Desirable BMI range is 18.5 to 24.9 kg/m <sup>2</sup> . If waist circumference is greater than or equal to 35 inches in women or greater than or equal to 40 inches in men, initiate lifestyle changes and treatment strategies for metabolic syndrome.
<b>Diabetes management:</b> Goal HbA1c less than 7%	Appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose, as indicated by HbA1c. Treatment of other risks (eg, physical activity, weight management, blood pressure, and cholesterol management).
<b>Antiplatelet agents/anticoagulants:</b>	Start and continue indefinitely aspirin 75 to 162 mg/d if not contraindicated. Consider clopidogrel 75 mg/d or warfarin if aspirin is contraindicated. Manage warfarin to INR of 2.5 to 3.5 in post-STEMI patients when clinically indicated or for those not able to take aspirin or clopidogrel (Figure 7).
<b>Renin-Angiotensin-Aldosterone System Blockers:</b>	ACE inhibitors in all patients indefinitely; start, early in stable high-risk patients (anterior MI, previous MI, Killip class greater than or equal to II [S <sub>3</sub> gallop, rales, radiographic CHF], LVEF less than 0.40). ARBs in patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF less than 0.40. Aldosterone blockade in patients without significant renal dysfunction§ or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either diabetes or heart failure.
<b>Beta-Blockers:</b>	Start in all patients. Continue indefinitely. Observe usual contraindications.

BMI indicates body mass index; in, inches; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; INR, international normalization ratio; ACE, angiotensin converting enzyme; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; ARB, angiotensin receptor blocker and TG, triglycerides.

\*Non-HDL cholesterol equals total cholesterol minus HDL cholesterol.

†Treat to a goal of non-HDL-C substantially less than 130 mg/dL.

‡Dietary-supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should be used only if approved and monitored by a physician.

§Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women.

||Potassium should be less than or equal to 5.0 mEq/L.

Modified with permission from Smith et al. *Circulation*. 2004;109:672–93.<sup>18</sup>

#### **4. Smoking Cessation**

##### **Class I**

- 1. Patients recovering from STEMI who have a history of cigarette smoking should be strongly encouraged to stop smoking and to avoid secondhand smoke. Counseling should be provided to the patient and family, along with pharmacological therapy (including nicotine replacement and bupropion) and formal smoking-cessation programs as appropriate. (Level of Evidence: B)**
- 2. All STEMI patients should be assessed for a history of cigarette smoking. (Level of Evidence: A)**

##### **5. Antiplatelet Therapy**

##### **Class I**

- 1. A daily dose of aspirin 75 to 162 mg orally should be given indefinitely to patients recovering from STEMI. (Level of Evidence: A)**
- 2. If true aspirin allergy is present, preferably clopidogrel (75 mg orally per day) or, alternatively, ticlopidine (250 mg orally twice daily) should be substituted. (Level of Evidence: C)**
- 3. If true aspirin allergy is present, warfarin therapy with a target INR of 2.5 to 3.5 is a useful alternative to clopidogrel in patients less than 75 years of age who are at low risk for bleeding and who can be monitored adequately for dose adjustment to maintain a target INR range. (Level of Evidence: C)**

##### **Class III**

- 1. Ibuprofen should not be used because it blocks the antiplatelet effects of aspirin. (Level of Evidence: C)**

On the basis of 12 randomized trials in 18 788 patients with prior infarction, the Antiplatelet Trialists' Collaboration reported a 25% reduction in the risk of recurrent infarction, stroke, or vascular death in patients receiving prolonged antiplatelet therapy (36 fewer events for every 1000 patients treated).<sup>31</sup> No antiplatelet therapy has proved superior to aspirin in this population, and daily doses of aspirin between 80 and 325 mg appear to be effective.<sup>184</sup> The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, which compared aspirin with clopidogrel in 19 185 patients at high risk for vascular events, demonstrated a modest but significant (8.6%, *P* equals 0.043) reduction in serious vascular events with clopidogrel compared with aspirin.<sup>185</sup> These data suggest clopidogrel as the best alternative to aspirin in patients with true aspirin allergy.

The use of warfarin therapy for secondary prevention of vascular events in patients after STEMI is discussed in Section 7.12.11 of the full-text guidelines. Large randomized trials have demonstrated that oral anticoagulants, when given in adequate doses, reduce the rates of adverse outcomes, at the cost of a small increase in hemorrhagic events.<sup>186-188</sup> In the Warfarin, Aspirin, Reinfarction Study (WARIS II), warfarin without aspirin in a dose intended to achieve an INR of 2.8 to 4.2 resulted in a significant reduction in a composite end point (death, nonfatal reinfarction, or thromboembolic stroke) compared with therapy with aspirin alone (16.7%

versus 20.0%).<sup>186</sup> Warfarin therapy resulted in a small but significant increase in major, nonfatal bleeding compared with therapy with aspirin alone (0.62% versus 0.17% per year). Chronic therapy with warfarin after STEMI presents an alternative to clopidogrel in patients with aspirin allergy.

##### **6. Inhibition of Renin-Angiotensin-Aldosterone-System**

##### **Class I**

- 1. An ACE inhibitor should be prescribed at discharge for all patients without contraindications after STEMI. (Level of Evidence: A)**
- 2. Long-term aldosterone blockade should be prescribed for post-STMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either symptomatic heart failure or diabetes. (Level of Evidence: A)**
- 3. An ARB should be prescribed at discharge in those STEMI patients who are intolerant of an ACE inhibitor and have either clinical or radiological signs of heart failure and LVEF less than 0.40. Valsartan and candesartan have established efficacy for this recommendation. (Level of Evidence: B)**

##### **Class IIa**

- 1. In STEMI patients who tolerate ACE inhibitors, an ARB can be useful as an alternative to ACE inhibitors in the long-term management of STEMI patients, provided there are either clinical or radiological signs of heart failure or LVEF less than 0.40. Valsartan and candesartan have established efficacy for this recommendation. (Level of Evidence: B)**

##### **Class IIb**

- 1. The combination of an ACE inhibitor and an ARB may be considered in the long-term management of STEMI patients with persistent symptomatic heart failure and LVEF less than 0.40. (Level of Evidence: B)**

The use of ACE inhibitors early in the acute phase of STEMI and in the hospital management phase has been described earlier.

Compelling evidence now supports the broad long-term use of ACE inhibitors after STEMI.<sup>189,190</sup> The results of the VALIANT study (Valsartan in Acute Myocardial Infarction Trial) evaluating valsartan are discussed in Section 7.4.3 of the full-text guidelines. The series of CHARM studies (Candesartan in Heart Failure Assessment in Reduction of Mortality), although focusing on the evaluation of candesartan in patients with chronic heart failure, provides information that can be extrapolated to the long-term management of the STEMI patient, because 50% to 60% of the patients studied had ischemic heart disease as the cause of heart failure.<sup>191-193</sup>

Given the extensive randomized trial and routine clinical experience with ACE inhibitors, they remain the logical first

agent for inhibition of the renin-angiotensin-aldosterone system in the long-term management of patients with STEMI.<sup>150,194</sup> The ARBs valsartan and candesartan should be administered over the long term to STEMI patients with symptomatic heart failure who are intolerant of ACE inhibitors. As described in Section 7.4.3 of the full-text guidelines, the choice between an ACE inhibitor and an ARB over the long term in patients who are tolerant of ACE inhibitors will vary with individual physician and patient preference, as well as cost and anticipated side-effect profile.<sup>150,194</sup>

The results of the most relevant clinical trials that tested combinations of ACE inhibitors and ARBs have been subtly different, but clinically relevant. Whereas the CHARM-Added<sup>192</sup> trial demonstrated a reduction in the combined end point of heart failure hospitalization and death over ACE inhibition alone, the VALIANT study<sup>149</sup> reported that the combination of captopril and valsartan was equivalent to either alone, but with a greater number of adverse effects. Thus, when combination ACE inhibition and angiotensin receptor blockade is considered necessary, the preferred ARB is candesartan. Although there is evidence that the combination of an ACE inhibitor and an aldosterone inhibitor is effective at reducing mortality and is well tolerated in patients with a serum creatinine level of 2.5 mg/dL or less and a serum potassium concentration of 5.0 mEq/L or less (see Section 7.4.3 of the full-text guidelines), much less experience exists with the combination of an ARB and aldosterone inhibitor (24% of 2028 patients in the CHARM-Alternative trial)<sup>191</sup> and the triple combination of an ACE inhibitor, ARB, and an aldosterone antagonist (17% of 2548 patients in the CHARM-Added trial).<sup>192</sup>

The combination of an ACE inhibitor and an ARB (valsartan 20 mg/d orally initially; titrated up to 160 mg orally twice per day, or candesartan 4 to 8 mg/d orally initially; titrated up to 32 mg/d orally) or an ACE inhibitor and an aldosterone inhibitor may be considered for the long-term management of STEMI patients with symptomatic heart failure and LVEF less than 0.40, provided the serum creatinine level is less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women and the serum potassium concentration is less than or equal to 5.0 mEq/L (See Sections 7.4.3 and 7.6.4 of the full-text guidelines.)

## **7. Beta-Blockers**

### **Class I**

- All patients after STEMI except those at low risk (normal or near-normal ventricular function, successful reperfusion, and absence of significant ventricular arrhythmias) and those with contraindications should receive beta-blocker therapy. Treatment should begin within a few days of the event, if not initiated acutely, and continue indefinitely. (Level of Evidence: A)**
- Patients with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme. (Level of Evidence: B)**

### **Class IIa**

- It is reasonable to prescribe beta-blockers to low-risk patients after STEMI who have no contraindications to that class of medications. (Level of Evidence: A)**

The use of beta-blockers in the early phase of STEMI and in hospital management is reviewed in Sections 6.3.1.6 and 7.4.1 of the full-text guidelines. The benefits of beta-blocker therapy in patients without contraindications have been demonstrated with or without reperfusion, initiated early or later in the clinical course, and for all age groups. The benefits of beta-blocker therapy for secondary prevention are well established.<sup>142,196</sup> In patients with moderate or severe LV failure, beta-blocker therapy should be administered with a gradual titration scheme.<sup>197</sup> Long-term beta-blocker therapy should be administered to survivors of STEMI who have subsequently undergone revascularization, because there is evidence of a mortality benefit from their use despite revascularization with either CABG surgery or PCI.<sup>198</sup>

## **8. Blood Pressure Control**

### **Class I**

- Blood pressure should be treated with drug therapy to a target level of less than 140/90 mm Hg and to less than 130/80 mm Hg for patients with diabetes or chronic kidney disease. (Level of Evidence: B)**
- Lifestyle modification (weight control, dietary changes, physical activity, and sodium restriction) should be initiated in all patients with blood pressure greater than or equal to 120/80 mm Hg. (Level of Evidence: B)**

### **Class IIb**

- A target blood pressure goal of 120/80 mm Hg for post-STEMI patients may be reasonable. (Level of Evidence: C)**

### **Class III**

- Short-acting dihydropyridine calcium channel blocking agents should not be used for the treatment of hypertension. (Level of Evidence: B)**

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)<sup>199</sup> recommends that patients be treated after MI with ACE inhibitors, beta-blockers, and, if necessary, aldosterone antagonists to a target blood pressure of less than 140/90 mm Hg, or less than 130/80 mm Hg for those with chronic kidney disease or diabetes.<sup>199</sup> Most patients will require 2 or more drugs to reach this goal, and when the blood pressure is greater than 20/10 mm Hg above goal, 2 drugs should usually be used from the outset.

JNC-7 emphasizes the importance of lifestyle modifications for all patients with blood pressure of 120/80 mm Hg or greater.<sup>199</sup> These modifications include weight reduction if overweight or obese, consumption of a diet rich in fruits and vegetables and low in total fat and saturated fat, and reduction of sodium to no more than 2.4 g/d.<sup>199</sup>

**9. Diabetes Management****Class I**

- Hypoglycemic therapy should be initiated to achieve HbA1c less than 7%. (Level of Evidence: B)**

**Class III**

- Thiazolidinediones should not be used in patients recovering from STEMI who have New York Heart Association class III or IV heart failure. (Level of Evidence: B)**

**10. Hormone Therapy****Class III**

- Hormone therapy with estrogen plus progestin should not be given de novo to postmenopausal women after STEMI for secondary prevention of coronary events. (Level of Evidence: A)**
- Postmenopausal women who are already taking estrogen plus progestin at the time of a STEMI should not continue hormone therapy. However, women who are beyond 1 to 2 years after initiation of hormone therapy who wish to continue hormone therapy for another compelling indication should weigh the risks and benefits, recognizing a greater risk of cardiovascular events. However, hormone therapy should not be continued while patients are on bedrest in the hospital. (Level of Evidence: B)**

On the basis of the Heart and Estrogen/progestin Replacement Study (HERS),<sup>200</sup> the Heart and Estrogen/progestin Replacement Study Follow-up (HERS-2),<sup>201</sup> and the Women's Health Initiative,<sup>202</sup> postmenopausal women should not receive combination estrogen and progestin therapy for primary or secondary prevention of CHD. It is recommended that the use of hormone therapy be discontinued in women who have STEMI.<sup>200–202</sup>

**11. Warfarin Therapy****Class I**

- Warfarin should be given to aspirin-allergic post-STEMI patients with indications for anticoagulation as follows:**
  - Without stent implanted (INR 2.5 to 3.5). (Level of Evidence: B)**
  - With stent implanted and clopidogrel 75 mg/d administered concurrently (INR 2.0 to 3.0). (Level of Evidence: C)**
- Warfarin (INR 2.5 to 3.5) is a useful alternative to clopidogrel in aspirin-allergic patients after STEMI who do not have a stent implanted. (Level of Evidence: B)**
- Warfarin (INR 2.0 to 3.0) should be prescribed for post-STEMI patients with either persistent or paroxysmal atrial fibrillation. (Level of Evidence: A)**
- In post-STEMI patients with LV thrombus noted on an imaging study, warfarin should be prescribed for at least 3 months (Level of Evidence: B) and indefinitely in patients without an increased risk of bleeding (Level of Evidence: C).**

- Warfarin alone (INR 2.5 to 3.5) or warfarin (INR 2.0 to 3.0) in combination with aspirin (75 to 162 mg) should be prescribed in post-STEMI patients who have no stent implanted and who have indications for anticoagulation. (Level of Evidence: B)**

**Class IIa**

- In post-STEMI patients less than 75 years of age without specific indications for anticoagulation who can have their level of anticoagulation monitored reliably, warfarin alone (INR 2.5 to 3.5) or warfarin (INR 2.0 to 3.0) in combination with aspirin (75 to 162 mg) can be useful for secondary prevention. (Level of Evidence: B)**
- It is reasonable to prescribe warfarin to post-STEMI patients with LV dysfunction and extensive regional wall-motion abnormalities. (Level of Evidence: A)**

**Class IIb**

- Warfarin may be considered in patients with severe LV dysfunction, with or without CHF. (Level of Evidence: C)**

The indications for long-term anticoagulation after STEMI remain controversial and are evolving. Although the use of warfarin has been demonstrated to be cost-effective compared with standard therapy without aspirin, the superior safety, efficacy and cost-effectiveness of aspirin has made it the antithrombotic agent of choice for secondary prevention<sup>203</sup> (Figure 7).

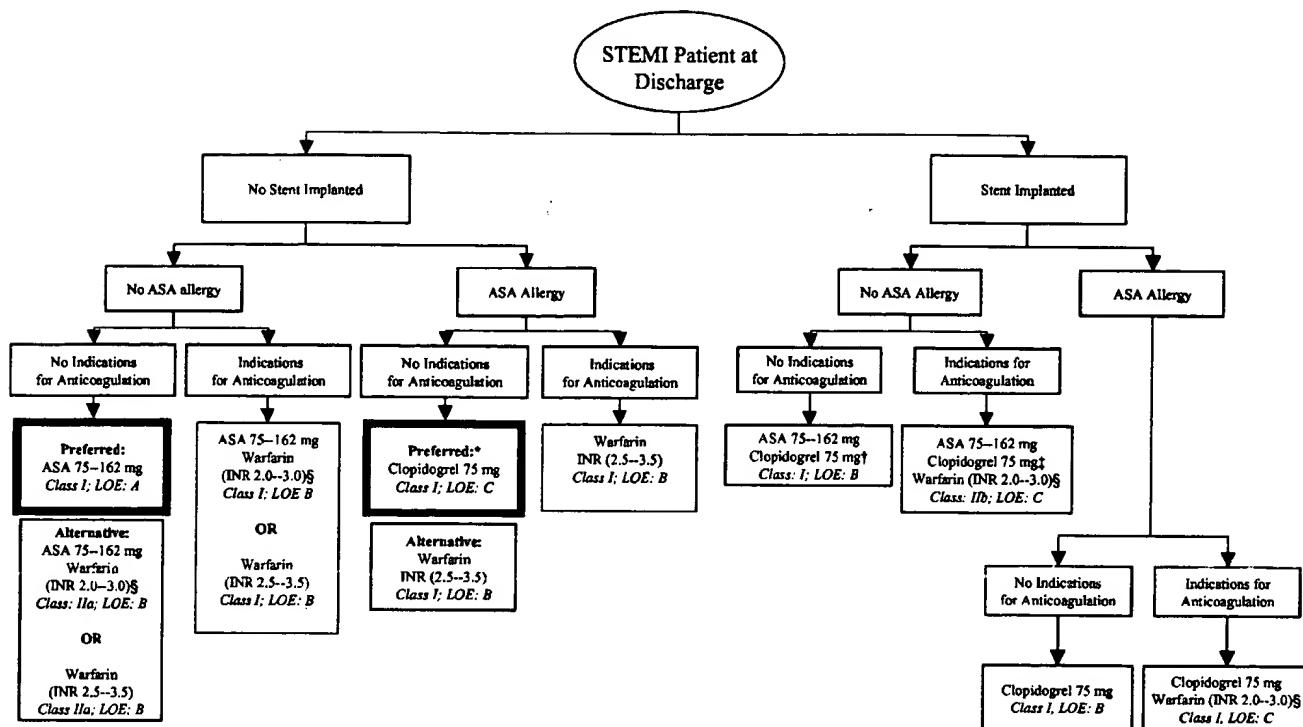
**12. Physical Activity****Class I**

- On the basis of assessment of risk, ideally with an exercise test to guide the prescription, all patients recovering from STEMI should be encouraged to exercise for a minimum of 30 minutes, preferably daily but at least 3 or 4 times per week (walking, jogging, cycling, or other aerobic activity), supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, and household work). (Level of Evidence: B)**
- Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. (Level of Evidence: C)**

**13. Antioxidants****Class III**

- Antioxidant vitamins such as vitamin E and/or vitamin C supplements should not be prescribed to patients recovering from STEMI to prevent cardiovascular disease. (Level of Evidence: A)**

There is no convincing evidence to support lipid- or water-soluble antioxidant supplementation in patients after STEMI or patients with or without established coronary disease.



**Figure 7.** Long-term antithrombotic therapy at hospital discharge after STEMI. ASA indicates aspirin; LOE, level of evidence LV, left ventricular; and INR, international normalized ratio. \*Clopidogrel is preferred over warfarin because of increased risk of bleeding and low patient compliance in warfarin trials. †For 12 months. ‡Discontinue clopidogrel 1 month after implantation of a bare metal stent or several months after implantation of a drug-eluting stent (3 months after sirolimus and 6 months after paclitaxel) because of the potential increased risk of bleeding with warfarin and 2 antiplatelet agents. Continue aspirin and warfarin long term if warfarin is indicated for other reasons such as atrial fibrillation, LV thrombus, cerebral emboli, or extensive regional wall-motion abnormality. §An INR of 2.0 to 3.0 is acceptable with tight control, but the lower end of this range is preferable. The combination of antiplatelet therapy and warfarin may be considered in patients aged less than 75 years with low bleeding risk who can be monitored reliably.

## VIII. Long-Term Management

### A. Psychosocial Impact of STEMI

#### Class I

1. The psychosocial status of the patient should be evaluated, including inquiries regarding symptoms of depression, anxiety, or sleep disorders and the social support environment. (Level of Evidence: C)

#### Class IIa

1. Treatment with cognitive-behavioral therapy and selective serotonin reuptake inhibitors can be useful for STEMI patients with depression that occurs in the year after hospital discharge. (Level of Evidence: A)

Treatment of depression with combined cognitive-behavioral therapy and selective serotonin reuptake inhibitors improves outcome in terms of depression symptoms and social function.<sup>204–206</sup> It appears prudent to assess STEMI patients for depression during hospitalization and during the first month after STEMI and to intervene and reassess yearly in the first 5 years, as appropriate. There is evidence that the STEMI experience, with its sudden and unexpected onset, dramatic changes in lifestyle, and the additive effort of comorbid life events, is a relatively traumatic event and may produce impaired coping during subsequent ischemic events.<sup>207</sup>

### B. Cardiac Rehabilitation

#### Class IIa

1. Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. (Level of Evidence: C)

### C. Follow-Up Visit With Medical Provider

#### Class I

1. A follow-up visit should delineate the presence or absence of cardiovascular symptoms and functional class. (Level of Evidence: C)
2. The patient's list of current medications should be reevaluated in a follow-up visit, and appropriate titration of ACE inhibitors, beta-blockers, and statins should be undertaken. (Level of Evidence: C)
3. The predischarge risk assessment and planned workup should be reviewed and continued (Figure 6). This should include a check of LV function and possibly Holter monitoring for those patients whose early post-STEMI ejection fraction was 0.31 to 0.40 or lower, in consideration of possible ICD use (Figure 5). (Level of Evidence: C)
4. The healthcare provider should review and emphasize the principles of secondary prevention with the

- patient and family members (Table 4).<sup>181</sup> (*Level of Evidence: C*)
5. The psychosocial status of the patient should be evaluated in follow-up, including inquiries regarding symptoms of depression, anxiety, or sleep disorders and the social support environment. (*Level of Evidence: C*)
  6. In a follow-up visit, the healthcare provider should discuss in detail issues of physical activity, return to work, resumption of sexual activity, and travel, including driving and flying. The metabolic equivalent values for various activities are provided as a resource in Table 34 of the full-text guideline. (*Level of Evidence: C*)
  7. Patients and their families should be asked if they are interested in CPR training after the patient is discharged from the hospital. (*Level of Evidence: C*)
  8. Providers should actively review the following issues with patients and their families:
    - a. The patient's heart attack risk. (*Level of Evidence: C*)
    - b. How to recognize symptoms of STEMI. (*Level of Evidence: C*)
    - c. The advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 minutes, despite feelings of uncertainty about the symptoms and fear of potential embarrassment. (*Level of Evidence: C*)
    - d. A plan for appropriate recognition and response to a potential acute cardiac event, including the phone number to access EMS, generally 9-1-1.<sup>15</sup> (*Level of Evidence: C*)
  9. Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. (*Level of Evidence: C*)

## References

1. Mehta RH, Montoye CK, Gallogly M, et al., for the GAP Steering Committee of the American College of Cardiology. Improving quality of care for acute myocardial infarction: The Guidelines Applied in Practice (GAP) Initiative. *JAMA*. 2002;287:1269–1276.
2. Jencks SF, Huff ED, Cuerdon T. Change in the quality of care delivered to medicare beneficiaries, 1998–1999 to 2000–2001. *JAMA*. 2003;289:305–312.
3. Schneider EC, Zaslavsky AM, Epstein AM. Racial disparities in the quality of care for enrollees in medicare managed care. *JAMA*. 2002;287:1288–1294.
4. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol*. 2000;36:2056–2063.
5. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, TX: American Heart Association 2003.
- 5a. Wiviott SD, Morrow DA, Giugliano RP, et al. Performance of the thrombolysis in myocardial infarction risk index for early acute coronary syndrome in the National Registry of Myocardial Infarction: a simple risk index predicts mortality in both ST and non-ST elevation myocardial infarction. *J Am Coll Cardiol* 2003;41:365A–366A.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
7. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.
8. National, Heart, Lung, and Blood Institute. *Act in Time to Heart Attack*. Available at: <http://www.nhlbi.nih.gov/actintime>, 2003. Accessed May 15, 2003.
9. American College of Cardiology. *Guidelines Applied in Practice*. Available at: <http://www.acc.org/gap/gap.htm>. Accessed May 15, 2003.
10. American Heart Association. *Get With the Guidelines*. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=1165>. Accessed May 15, 2003.
11. Topol EJ, Kereiakes DJ. Regionalization of care for acute ischemic heart disease: a call for specialized centers. *Circulation*. 2003;107:1463–1466.
12. Califf RM, Faxon DP. Need for centers to care for patients with acute coronary syndromes. *Circulation*. 2003;107:1467–1470.
13. Willerson JT. Editor's commentary: centers of excellence. *Circulation*. 2003;107:1471–1472.
14. National Cholesterol Education Program. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. NIH publication No. 02-5125. Bethesda, Md: National Heart, Lung, and Blood Institute, 2002. Guidelines, Related Tools, and Patient Information, available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Accessed April 12, 2003.
15. Dracup K, Alonso AA, Atkins JM, et al. The physician's role in minimizing prehospital delay in patients at high risk for acute myocardial infarction: recommendations from the National Heart Attack Alert Program. Working Group on Educational Strategies to Prevent Prehospital Delay in Patients at High Risk for Acute Myocardial Infarction. *Ann Intern Med*. 1997;126:645–651.
16. Hedges JR, Feldman HA, Bittner V, et al, for the REACT Study Group. Impact of community intervention to reduce patient delay time on use of reperfusion therapy for acute myocardial infarction: Rapid Early Action for Coronary Treatment (REACT) trial. *Acad Emerg Med*. 2000;7:862–872.
17. Canto JG, Zalenski RJ, Ornato JP, et al, for the National Registry of Myocardial Infarction 2 Investigators. Use of emergency medical services in acute myocardial infarction and subsequent quality of care: observations from the National Registry of Myocardial Infarction 2. *Circulation*. 2002;106:3018–3023.
18. Goldberg R, Goff D, Cooper L, et al. Age and sex differences in presentation of symptoms among patients with acute coronary disease: the Trial: Rapid Early Action for Coronary Treatment (REACT). *Coron Artery Dis*. 2000;11:399–407.
19. Hutchings CB, Mann NC, Daya M, et al, for the Rapid Early Action for Coronary Treatment Study. Patients with chest pain calling 9-1-1 or self-transporting to reach definitive care: which mode is quicker? *Am Heart J*. 2004;147:35–41.
20. Faxon D, Lenfant C. Timing is everything: motivating patients to call 9-1-1 at onset of acute myocardial infarction. *Circulation*. 2001;104:1210–1211.
21. US Department of Health and Human Services, Public Health Service, National Institutes of Health. National Heart, Lung, and Blood Institute. NIH publication No. 01-3313. September 2001. Available at: <http://www.nhlbi.nih.gov/health/prof/heart/mi/provider.pdf>. Accessed December 16, 2002.
22. Eisenberg MJ, Topol EJ. Prehospital administration of aspirin in patients with unstable angina and acute myocardial infarction. *Arch Intern Med*. 1996;156:1506–1510.
23. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343:311–322.
24. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet*. 1986;1:397–402.
25. Armstrong PW, Collen D, Antman E. Fibrinolysis for acute myocardial infarction: the future is here and now. *Circulation*. 2003;107:2533–2537.
26. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: Part 7: the era of reperfusion: section 1: acute coronary syndromes (acute myocardial infarction). *Circulation*. 2000;102(suppl 1):I-172-I-203.
27. Pedley DK, Bissett K, Connolly EM, et al. Prospective observational cohort study of time saved by prehospital thrombolysis for ST elevation myocardial infarction delivered by paramedics. *BMJ*. 2003;327:22–26.

28. Menown IB, Mackenzie G, Adgey AA. Optimizing the initial 12-lead electrocardiographic diagnosis of acute myocardial infarction. *Eur Heart J.* 2000;21:275-283.
29. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation.* 2003;108:2543-2549.
30. Come PC, Pitt B. Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. *Circulation.* 1976; 54:624-628.
31. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71-86.
32. Sagar KA, Smyth MR. A comparative bioavailability study of different aspirin formulations using on-line multidimensional chromatography. *J Pharm Biomed Anal.* 1999;21:383-392.
33. De Luca G, Suryapranata H, Zijlstra F, et al, for the ZWOLLE Myocardial Infarction Study Group. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol.* 2003;42:991-997.
34. Boersma E, Mercado N, Poldermans D, et al. Acute myocardial infarction. *Lancet.* 2003;361:847-858.
35. De Luca G, Suryapranata H, Ottenvanger JP, et al. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation.* 2004;109: 1223-1225.
36. Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996;348:771-775.
37. Zeymer U, Tebbe U, Essen R, et al, for the ALKK-Study Group. Influence of time to treatment on early infarct-related artery patency after different thrombolytic regimens. *Am Heart J.* 1999;137:34-38.
38. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy: the Myocardial Infarction Triage and Intervention Trial. *JAMA.* 1993;270:1211-1216.
39. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol.* 1998;32:1312-1319.
40. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion on outcomes with primary coronary angioplasty for acute myocardial infarction (results from the Stent Primary Angioplasty in Myocardial Infarction Trial). *Am J Cardiol.* 2001;88:1085-1090.
41. Williams DO. Treatment delayed is treatment denied. *Circulation.* 2004; 109:1806-1808.
42. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2003;24:28-66.
43. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation.* 2000;102: 2031-2037.
44. Lee KL, Woodlief LH, Topol EJ, et al, for the GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation.* 1995;91:1659-1668.
45. Morrow DA, Antman EM, Giugliano RP, et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet.* 2001;358:1571-1575.
46. Krumholz HM, Chen J, Wang Y, et al. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation.* 1999;99:2986-2992.
47. Granger CB, Goldberg RJ, Dabbous O, et al, for the Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med.* 2003; 163:2345-2353.
48. Magid DJ, Calonge BN, Rumsfeld JS, et al, for the National Registry of Myocardial Infarction 2 and 3 Investigators. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA.* 2000; 284:3131-3138.
49. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol.* 2003;92:824-826.
50. Bonnefoy E, Lapostolle F, Leizorovicz A, et al, for the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet.* 2002; 360:825-829.
51. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation.* 2003;108:2851-2856.
52. Widimsky P, Budesinsky T, Vorac D, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial: PRAGUE-2. *Eur Heart J.* 2003;24:94-104.
53. Deleted in press.
54. Antman EM. General hospital management. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction.* London, England: WB Saunders 1994;42-44.
- 54a. Lincoff AM, Califf RM, Van de Werf F, et al, for the Global Use of Strategies To Open Coronary Arteries (GUSTO) Investigators. Mortality at 1 year with combination platelet glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic therapy vs conventional fibrinolytic therapy for acute myocardial infarction: GUSTO V randomized trial. *JAMA.* 2002;288:2130-2135.
55. Zijlstra F, Beukema WP, van't Hof AW, et al. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. *J Am Coll Cardiol.* 1997;29:908-912.
56. Ribeiro EE, Silva LA, Carneiro R, et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol.* 1993;22:376-380.
57. Grinfield L, Berrocal D, Bellardi J, et al. Fibrinolysis versus primary angioplasty in acute myocardial infarction (FAP): a randomized trial in a community hospital in Argentina. *J Am Coll Cardiol.* 1996;27:A222. Abstract.
58. Zijlstra F, de Boer MJ, Hoornste JC, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med.* 1993;328:680-684.
59. Widimsky P, Groch L, Zelizko M, et al. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory: the PRAGUE study. *Eur Heart J.* 2000;21:823-831.
60. de Boer MJ, Ottenvanger JP, van't Hof AW, et al, for the Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and thrombolytic therapy. *J Am Coll Cardiol.* 2002; 39:1723-1728.
61. Akhras F, Ousa AA, Swann G, et al. Primary coronary angioplasty or intravenous thrombolysis for patients with acute myocardial infarction? Acute and late follow-up results in a new cardiac unit. *J Am Coll Cardiol.* 1997;29:A235-A236. Abstract.
62. Deleted in press.
63. Grines CL, Browne KF, Marco J, et al, for the Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1993;328:673-679.
64. Gibbons RJ, Holmes DR, Reeder GS, et al, for the Mayo Coronary Care Unit and Catheterization Laboratory Groups. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med.* 1993; 328:685-691.
65. Ribichini F, Steffenino G, Dellavalle A, et al. Comparison of thrombolytic therapy and primary coronary angioplasty with liberal stenting for inferior myocardial infarction with precordial ST-segment depression: immediate and long-term results of a randomized study. *J Am Coll Cardiol.* 1998;32:1687-1694.
66. García E, Elizaga J, Pérez-Castellano N, et al. Primary angioplasty versus systemic thrombolysis in anterior myocardial infarction. *J Am Coll Cardiol.* 1999;33:605-611.
67. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with

- tissue plasminogen activator for acute myocardial infarction. *N Engl J Med.* 1997;336:1621–1628.
68. Le May MR, Labinaz M, Davies RF, et al. Stenting versus thrombolysis in acute myocardial infarction trial (STAT). *J Am Coll Cardiol.* 2001; 37:985–991.
  69. Schömig A, Kastrati A, Dirschinger J, et al, for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. *N Engl J Med.* 2000;343:385–391.
  70. Vermeer F, Oude Ophuis AJ, vd Berg EJ, et al. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart.* 1999;82: 426–431.
  71. Kastrati A, Mehilli J, Dirschinger J, et al, for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOPAMI-2) Study. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2002;359:920–925.
  72. Andersen HR, Nielsen TT, Rasmussen K, et al, for the DANAMI-2 Investigators. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA.* 2002;287:1943–1951.
  73. Kastrati A, Mehilli J, Dirschinger J, et al, for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction (STOPAMI-2) Study. A randomized trial of transfer for primary angioplasty versus on-site thrombolysis in patients with high-risk myocardial infarction: the Air Primary Angioplasty in Myocardial Infarction study. *J Am Coll Cardiol.* 2002;39:1713–1719.
  74. Andersen HR, Nielsen TT, Rasmussen K, et al, for the DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med.* 2003;349: 733–742.
  75. Hochman JS, Sleeper LA, Webb JG, et al, for the Should We Emergency Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) Investigators. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med.* 1999;341: 625–634.
  76. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13–20.
  - 76a. Melandri G. The obsession with primary angioplasty. *Circulation.* 2003; 108:e1620.
  77. Rogers WJ, Dean LS, Moore PB, et al, for the Alabama Registry of Myocardial Ischemia Investigators. Comparison of primary angioplasty versus thrombolytic therapy for acute myocardial infarction. *Am J Cardiol.* 1994;74:111–118.
  78. Every NR, Parsons LS, Hlatky M, et al, for the Myocardial Infarction Triage and Intervention Investigators. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. *N Engl J Med.* 1996;335:1253–1260.
  79. Tiefenbrunn AJ, Chandra NC, French WJ, et al. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol.* 1998; 31:1240–1245.
  80. Danchin N, Vaur L, Genès N, et al. Treatment of acute myocardial infarction by primary coronary angioplasty or intravenous thrombolysis in the "real world": one-year results from a nationwide French survey. *Circulation.* 1999;99:2639–2644.
  81. Berger PB, Ellis SG, Holmes DR, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation.* 1999;100:14–20.
  82. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA.* 2000; 283:2941–2947.
  83. Brodie BR, Stuckey TD, Hansen C, et al. Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. *Am J Cardiol.* 2000;85:13–18.
  84. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation.* 2001;104:636–641.
  85. Clements IP, Christian TF, Higano ST, et al. Residual flow to the infarct zone as a determinant of infarct size after direct angioplasty. *Circulation.* 1993;88:1527–1533.
  86. Juliard JM, Feldman IJ, Golmärd JL, et al. Relation of mortality of primary angioplasty during acute myocardial infarction to door-to-Thrombolysis In Myocardial Infarction (TIMI) time. *Am J Cardiol.* 2003;91:1401–1405.
  87. Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. *Ann Intern Med.* 1991;115:173–177.
  88. Brodie BR, Weintraub RA, Stuckey TD, et al. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. *Am J Cardiol.* 1991;67:7–12.
  89. Hibert D, Juliard JM, Steg PG, et al. Primary coronary angioplasty for acute myocardial infarction with contraindication to thrombolysis. *Am J Cardiol.* 1993;71:377–381.
  90. Zahn R, Schuster S, Schiele R, et al, for the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. Comparison of primary angioplasty with conservative therapy in patients with acute myocardial infarction and contraindications for thrombolytic therapy. *Cathet Cardiovasc Interv.* 1999;46:127–133.
  91. Grzybowski M, Clements EA, Parsons L, et al. Mortality benefit of immediate revascularization of acute ST-segment elevation myocardial infarction in patients with contraindications to thrombolytic therapy: a propensity analysis. *JAMA.* 2003;290:1891–1898.
  92. Lotfi M, Mackie K, Dzavik V, et al. Impact of delays to cardiac surgery after failed angioplasty and stenting. *J Am Coll Cardiol.* 2004;43: 337–342.
  93. Dehmer GJ, Gantt DS. Coronary intervention at hospitals without on-site cardiac surgery: are we pushing the envelope too far? *J Am Coll Cardiol.* 2004;43:343–345.
  94. Antonucci D, Santoro GM, Bolognesi L, et al. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction: results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. *J Am Coll Cardiol.* 1998;31:1234–1239.
  95. Rodríguez A, Bernardi V, Fernández M, et al. In-hospital and late results of coronary stents versus conventional balloon angioplasty in acute myocardial infarction: Gianturco-Roubin in Acute Myocardial Infarction (GRAMI) trial. *Am J Cardiol.* 1998;81:1286–1291.
  96. Suryapranata H, Ottenvanger JP, Nibbering E, et al. Long term outcome and cost-effectiveness of stenting versus balloon angioplasty for acute myocardial infarction. *Heart.* 2001;85:667–671.
  97. Saito S, Hosokawa G, Tanaka S, et al, for the PASTA Trial Investigators. Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the primary angioplasty versus stent implantation in acute myocardial infarction (PASTA) trial. *Cathet Cardiovasc Interv.* 1999;48:262–268.
  98. Grines CL, Cox DA, Stone GW, et al, for the Stent Primary Angioplasty in Myocardial Infarction Study Group. Coronary angioplasty with or without stent implantation for acute myocardial infarction. *N Engl J Med.* 1999;341:1949–1956.
  99. Kawashima A, Ueda K, Nishida Y, et al. Quantitative angiographic analysis of restenosis of primary stenting using Wiktor stent for acute myocardial infarction: results from a multicenter randomized PRISAM study. *Circulation.* 1999;100(suppl 1):I-856. Abstract.
  100. Maillard L, Harmon M, Khalife K, et al, for the STENTIM-2 Investigators. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. *J Am Coll Cardiol.* 2000;35: 1729–1736.
  101. Scheller B, Hennen B, Severin-Kneib S, et al. Long-term follow-up of a randomized study of primary stenting versus angioplasty in acute myocardial infarction. *Am J Med.* 2001;110:1–6.
  102. Zhu MM, Feit A, Chadow H, et al. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. *Am J Cardiol.* 2001;88:297–301.

103. Stone GW, Grines CL, Cox DA, et al, for the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med.* 2002;346:957–966.
104. Lemos PA, Saia F, Hofma SH, et al. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol.* 2004; 43:704–708.
- 104a. Ellis SG, Armstrong P, Betriu A, et al. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial. *Am Heart J.* 2004; 147:E16.
105. The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI II A results. *JAMA.* 1988;260:2849–2858.
106. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med.* 1987;317:581–588.
107. Sadanandan S, Buller C, Menon V, et al. The late open artery hypothesis: a decade later. *Am Heart J.* 2001;142:411–421.
108. Hochman JS, Sleeper LA, White HD, et al, for the SHOCK Investigators: Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock: one-year survival following early revascularization for cardiogenic shock. *JAMA.* 2001;285:190–192.
109. Dzavik V, Sleeper LA, Cocke TP, et al, for the SHOCK Investigators. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: a report from the SHOCK Trial Registry. *Eur Heart J.* 2003;24:828–837.
110. Dauerman HL, Goldberg RJ, Malinski M, et al. Outcomes and early revascularization for patients greater than or equal to 65 years of age with cardiogenic shock. *Am J Cardiol.* 2001;87:844–848.
111. Dauerman HL, Ryan TJ, Piper WD, et al. Outcomes of percutaneous coronary intervention among elderly patients in cardiogenic shock: a multicenter, decade-long experience. *J Invasive Cardiol.* 2003;15:380–384.
112. Simoons ML, Arnold AE, Betriu A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet.* 1988;1:197–203.
113. Ross AM, Coyne KS, Reiner JS, et al, for the PACT (Plasminogen-activator Angioplasty Compatibility Trial). Investigators: A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. *J Am Coll Cardiol.* 1999;34: 1954–1962.
114. Montalescot G, Barragan P, Wittenberg O, et al, for the ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up). Investigators. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med.* 2001;344:1895–1903.
115. Zeymer U, Uebis R, Vogt A, et al, for the ALKK-Study Group. Randomized comparison of percutaneous transluminal coronary angioplasty and medical therapy in stable survivors of acute myocardial infarction with single-vessel disease: a study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte. *Circulation.* 2003;108:1324–1328.
116. Scheller B, Hennen B, Hammer B, et al, for the SIAM III Study Group. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol.* 2003;42:634–641.
117. Braunwald E, Antman E, Beasley J, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol.* 2002;40:1366.
118. Stenstrand U, Wallentin L. Early revascularisation and 1-year survival in 14-day survivors of acute myocardial infarction: a prospective cohort study. *Lancet.* 2002;359:1805–1811.
119. Alter DA, Tu JV, Austin PC, et al. Waiting times, revascularization modality, and outcomes after acute myocardial infarction at hospitals with and without on-site revascularization facilities in Canada. *J Am Coll Cardiol.* 2003;42:410–419.
120. Gupta M, Chang WC, Van de Werf F, et al, for the ASSENT II Investigators. International differences in in-hospital revascularization and outcomes following acute myocardial infarction: a multilevel analysis of patients in ASSENT-2. *Eur Heart J.* 2003;24:1640–1650.
121. Gibson CM, Karha J, Murphy SA, et al, for the TIMI Study Group. Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the thrombolysis in myocardial infarction trials. *J Am Coll Cardiol.* 2003;42:7–16.
122. Lablanche JM, Gueret P, Blanchard D, et al. Beneficial effects of very early PTCA in patients with intravenous thrombolysis for acute myocardial infarction: data from a nation-wide registry in France. *Circulation.* 2002;106(suppl II):II-630. Abstract.
123. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al. Prospective randomized trial comparing a routine invasive strategy within 24 hours to thrombolysis versus an ischemia-guided conservative approach to acute myocardial infarction with ST-segment elevation: the Gracia-1 trial. *Lancet.* 2004. In press.
124. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet.* 1988;2:349–360.
125. Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation.* 1996;93:870–878.
126. White HD, Yusuf S. Issues regarding the use of heparin following streptokinase therapy. *J Thromb Thrombolysis.* 1995;2:5–10.
127. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet.* 2001;358:1855–1863.
128. Bertrand ME, Rupprecht HJ, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation.* 2000;102:624–629.
129. Mehta SR, Yusuf S, Peters RJ, et al, for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527–533.
130. Steinhubl SR, Berger PB, Mann JT III, et al, for the CREDO (Clopidogrel for the Reduction of Events During Observation) Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002; 288:2411–2420.
131. CYPHER™ sirolimus-eluting coronary stent on RAPTOR™ over-the-wire delivery system and CYPHER™ sirolimus-eluting coronary stent on RAPTORRAIL® rapid exchange delivery system [instructions for use]. Miami, FL: Cordis, a Johnson & Johnson Company; April 2003.
132. TAXUS: paclitaxel-eluting coronary stent system Monorail and over the wire coronary stent delivery system [directions for use]. Natick, MA: Boston Scientific; March 2004.
133. Patrono C, Bachmann F, Baigent C, et al. Expert consensus document on the use of antiplatelet agents: The Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease of the European Society of Cardiology. *Eur Heart J.* 2004;25:166–181.
134. Levine GN, Kern MJ, Berger PB, et al, for the American Heart Association Diagnostic and Interventional Catheterization Committee and Council on Clinical Cardiology. Management of patients undergoing percutaneous coronary revascularization. *Ann Intern Med.* 2003;139:123–136.
135. Lee DP, Herity NA, Hiatt BL, et al, for the Tirofiban Given in the Emergency Room before Primary Angioplasty. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. *Circulation.* 2003;107:1497–1501.
136. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. *JAMA.* 2003;290:2041–2047.
- 136a. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care.* 2004;27:553–597.
137. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143–3421.
138. Malan SS. Psychosocial adjustment following MI: current views and nursing implications. *J Cardiovasc Nurs.* 1992;6:57–70.

139. Havik OE, Maeland JG. Patterns of emotional reactions after a myocardial infarction. *J Psychosom Res.* 1990;34:271-285.
140. Moser DK, Dracup K. Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? *Psychosom Med.* 1996;58:395-401.
141. Frasure-Smith N, Lespérance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychol.* 1995;14:388-398.
142. Chae Cu, Hennekens CH. Beta blockers. In: Hennekens CH, ed. *Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease*. Philadelphia, Pa: WB Saunders 1999;79-94.
143. Latini R, Maggioni AP, Flather M, et al. ACE inhibitor use in patients with myocardial infarction: summary of evidence from clinical trials. *Circulation.* 1995;92:3132-3137.
144. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation.* 1998;97:2202-2212.
145. Flather MD, Yusuf S, Køber L, et al, for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet.* 2000;355:1575-1581.
146. Pitt B, Zannad F, Remme WJ, et al, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med.* 1999;341:709-717.
147. Pitt B, Remme W, Zannad F, et al, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309-1321.
148. Dickstein K, Kjekshus J, for the OPTIMAAL Steering Committee of the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial: Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet.* 2002;360:752-760.
149. Pfeffer MA, McMurray JJ, Velazquez EJ, et al, for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med.* 2003;349:1893-1906.
150. Mann DL, Deswal A. Angiotensin-receptor blockade in acute myocardial infarction: a matter of dose. *N Engl J Med.* 2003;349:1963-1965.
151. Gibbons RJ, Miller TD, Christian TF. Infarct size measured by single photon emission computed tomographic imaging with (99m) Tc-sestamibi: a measure of the efficacy of therapy in acute myocardial infarction. *Circulation.* 2000;101:101-108.
152. Klocke FJ, Baird MG, Bateman TM, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Radionuclide Imaging). Available at: [http://www.acc.org/clinical/guidelines/rni\\_fulltext.pdf](http://www.acc.org/clinical/guidelines/rni_fulltext.pdf), 2003. Accessed January 15, 2004.
153. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Available at: [www.acc.org/clinical/guidelines/echo/index.pdf](http://www.acc.org/clinical/guidelines/echo/index.pdf), 2003. Accessed January 15, 2004.
154. Mahrholdt H, Wagner A, Holly TA, et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. *Circulation.* 2002;106:2322-2327.
155. Menon V, Slater JN, White HD, et al. Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. *Am J Med.* 2000;108:374-380.
156. Hochman JS, Boland J, Sleeper LA, et al, for the SHOCK Registry Investigators. Current spectrum of cardiogenic shock and effect of early revascularization on mortality: results of an International Registry. *Circulation.* 1995;91:873-881.
157. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). Available at: [http://www.acc.org/clinical/guidelines/failure/hf\\_index.htm](http://www.acc.org/clinical/guidelines/failure/hf_index.htm), 2001. Accessed June 5, 2004.
158. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med.* 1994;330:1211-1217.
159. Núñez L, de la Llana R, López Sendón J, et al. Diagnosis and treatment of subacute free wall ventricular rupture after infarction. *Ann Thorac Surg.* 1983;35:525-529.
160. Guidelines for cardiopulmonary resuscitation and emergency cardiac care: Emergency Cardiac Care Committee and Subcommittees, American Heart Association: Part III: adult advanced cardiac life support. *JAMA.* 1992;268:2199-2241.
161. Campbell RWF. Arrhythmias. In: Julian DG, Braunwald E, eds. *Management of Acute Myocardial Infarction*. London, England: WB Saunders 1994;223-240.
162. Kontoyannis DA, Anastasiou-Nana MI, Kontoyannis SA, et al. Intravenous amiodarone decreases the duration of atrial fibrillation associated with acute myocardial infarction. *Cardiovasc Drugs Ther.* 2001;15:155-160.
163. Ryan TJ, Antman EM, Brooks NH, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: 1999 guideline update: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol.* 1999;34:890-911.
164. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Am Coll Cardiol.* 2002;40:1703-1719.
165. Lamas GA, Ellenbogen KA. Evidence base for pacemaker mode selection: from physiology to randomized trials. *Circulation.* 2004;109:443-451.
166. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology/American Heart Association. *J Am Coll Cardiol.* 1999;34:1262-1347.
167. Dyke C, Bhatia D. Inhibitors of the platelet receptor glycoprotein IIb-IIIa and complications during percutaneous coronary revascularization: management strategies for the cardiac surgeon. *J Cardiovasc Surg (Torino).* 1999;40:505-516.
168. Yusuf S, Zhao F, Mehta SR, et al, for the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494-502.
169. Physician's Desk Reference. Clopidogrel package insert. Montvale, NJ: Medical Economics Co; 2756.
170. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Available at: [http://www.acc.org/clinical/guidelines/exercise/exercise\\_clean.pdf](http://www.acc.org/clinical/guidelines/exercise/exercise_clean.pdf), 2002. Accessed February 12, 2004.
171. Thérioux P, Waters DD, Halphen C, et al. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med.* 1979;301:341-345.
172. DeBusk RF, Kraemer HC, Nash E, et al. Stepwise risk stratification soon after acute myocardial infarction. *Am J Cardiol.* 1983;52:1161-1166.
173. Krone RJ, Gillespie JA, Weld FM, et al. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. *Circulation.* 1985;71:80-89.
174. Valentine PA, Frew JL, Mashford ML, et al. Lidocaine in the prevention of sudden death in the pre-hospital phase of acute infarction: a double-blind study. *N Engl J Med.* 1974;291:1327-1331.
175. Ross J, Gilpin EA, Madsen EB, et al. A decision scheme for coronary angiography after acute myocardial infarction. *Circulation.* 1989;79:292-303.
176. Risk stratification and survival after myocardial infarction. *N Engl J Med.* 1983;309:331-336.

177. Zaret BL, Wackers TH, Terrin M, et al. Does left ventricular ejection fraction following thrombolytic therapy have the same prognostic impact described in the prethrombolytic era? Results of the TIMI II Trial. *J Am Coll Cardiol.* 1991;17:214A. Abstract.
178. Roig E, Magnífica J, García A, et al. Prognostic value of exercise radionuclide angiography in low-risk acute myocardial infarction survivors. *Eur Heart J.* 1993;14:213-218.
179. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). Available at: [www.acc.org/clinical/guidelines/stable/stable.pdf](http://www.acc.org/clinical/guidelines/stable/stable.pdf). Accessed March 18, 2004.
180. O'Neill WW. "Watchful waiting" after thrombolysis: it's time for a re-evaluation. *J Am Coll Cardiol.* 2003;42:17-19.
181. Smith SC, Blair SN, Bonow RO, et al. AHA/ACC scientific statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation.* 2001;104:1577-1579.
182. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation.* 2004;109:672-693.
183. Dalal H, Evans PH, Campbell JL. Recent developments in secondary prevention and cardiac rehabilitation after acute myocardial infarction. *BMJ.* 2004;328:693-697.
184. Gutstein DE, Fuster V. Pathophysiologic bases for adjunctive therapies in the treatment and secondary prevention of acute myocardial infarction. *Clin Cardiol.* 1998;21:161-168.
185. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348:1329-1339.
186. Hurlen M, Smith P, Arnesen H. Effects of warfarin, aspirin and the two combined, on mortality and thromboembolic morbidity after myocardial infarction: the WARIS-II (Warfarin-Aspirin Reinfarction Study) design. *Scand Cardiovasc J.* 2000;34:168-171.
187. van Es RF, Jonker JJ, Verheugt FW, et al, for the Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet.* 2002;360:109-113.
188. Brouwer MA, van den Berg PJ, Aengevaeren WR, et al. Aspirin plus coumarin versus aspirin alone in the prevention of recrudescence after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Recrudescence In Coronary Thrombolysis (APRICOT)-2 Trial. *Circulation.* 2002;106:659-665.
189. Yusuf S, Sleight P, Pogue J, et al, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145-153.
190. Fox KM, for the EUROPean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPIDA study). *Lancet.* 2003;362:782-788.
191. Granger CB, McMurray JJ, Yusuf S, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet.* 2003;362:772-776.
192. McMurray JJ, Ostergren J, Swedberg K, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* 2003;362:767-771.
193. Yusuf S, Pfeffer MA, Swedberg K, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet.* 2003;362:777-781.
194. Executive Council of the Heart Failure Society of America. Implications of recent clinical trials for heart failure performance measures. *J Card Fail.* 2004;10:4-5.
195. Deleted in press.
196. Antman E, Braunwald E. Acute myocardial infarction. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine.* 6th ed. Philadelphia, Pa: WB Saunders;2001:1114-1251. Chapter 5.
197. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation.* 2003;107:1570-1575.
198. Chen J, Radford MJ, Wang Y, et al. Are beta-blockers effective in elderly patients who undergo coronary revascularization after acute myocardial infarction? *Arch Intern Med.* 2000;160:947-952.
199. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension.* 2003;41:1178-1179.
200. Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-613.
201. Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288:49-57.
202. Rossouw JE, Anderson GL, Prentice RL, et al, for the Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.
203. Cairns JA, Markham BA. Economics and efficacy in choosing oral anti-coagulants or aspirin after myocardial infarction. *JAMA.* 1995;273:965-967.
- 203a. Kris-Etherton PM, Lichtenstein AH, Howard BV, Steinberg D, Witzman JL. Antioxidant vitamin supplements and cardiovascular disease. *Circulation.* In press.
204. Glassman AH, O'Connor CM, Califf RM, et al, for the Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA.* 2002;288:701-709.
205. Swenson JR, O'Connor CM, Barton D, et al, for the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. Influence of depression and effect of treatment with sertraline on quality of life after hospitalization for acute coronary syndrome. *Am J Cardiol.* 2003;92:1271-1276.
206. Berkman LF, Blumenthal J, Burg M, et al, for the Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA.* 2003;289:3106-3116.
207. Alonso AA. Acute myocardial infarction and posttraumatic stress disorder: the consequences of cumulative adversity. *J Cardiovasc Nurs.* 1999;13:33-45.